EXHIBIT 36

Food and Drug Administration Office of Regulatory Affairs

Summary Report

For Sample Number: 454868

TD Sample Number: **Import Sample Number**

This is an accurate reproduction of the original electronic record as of 06/05/2008

Sample Class: Normal Everyday Sample
Sample Origin: Domestic
Sample Type: Official
Sample Basis: Surveillance
Home District:
Orig C/R and Records To: DAL-DO
Collecting District: ATL-DO
Collection PACs: 56008A

Product Name: Digoxin (Cardiotonic); Human - Rx/Single Ingredient; Prompt Release Tablets

Product Description: Digitek digoxin tablets, USP 250 mcg (0.25 mg) NDC 62794-146-01

Collection Reason: Sample collected as part of the FY2008 Low-cost Generic Drug Sample Survey (CP 7356.008) FACTS assignment # 896749 ORA concurrence # 2008101702

Lab: NRL **Split Num** 0 **Date Received:** 02/21/2008 **Date Out of Lab:** 06/05/2008

District Conclusion: **District Conclusion Made By:** **District**

Disposition Reason: **Disposition Authorized By:** **Disposition Authorized Date**

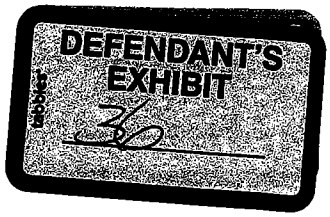
Performing Org	PAC	LID	PAF	Compliance No	Lab Class-Description	Laboratory Status
NRL-DCB-G	56008A		DRT		1 - In Compliance	Completed

Lab Conclusion

The sample meets USP specifications for Identification, Dissolution and Content Uniformity.

Lab Conclusion Date **Lab Conclusion Made By**

06/05/2008 Mathew,Samuel K



FLAG Original

ANALYST WORKSHEET	1. PRODUCT	2.. SAMPLE NUMBER
	DIGITEK (digoxin tablets, USP) 250 mcg (0.25 mg)	454866

3. SEALS	4. DATE REC'D	5. RECEIVED FROM	6. DISTRICT OF LABORATORY
☐ NONE ☒ INTACT ☐ BROKEN	2/27/08	Howard Lynch	NRL

7. DESCRIPTION OF SAMPLE

One clear, plastic bag officially sealed, "454866 2/15/08 Myoshi M. Francis Investigator ", containing two product bottles each identified " 454866 02/15/08 MMF ". An FDA 525 is attached to the sample.

8. NET CONTENTS			9. LABELING	
☐ NOT APPLICABLE ☒ NOT DETERMINED ___ UNITS EXAMINED	DECLARE/UNIT AMOUNT FOUND % OF DECLARED	100 tablets _____ _____		1 ORIGINAL(S) SUBMITTED _____ COPIES SUBMITTED ☐ NONE

10. SUMMARY OF ANALYSIS

Container: Round, opaque, white, plastic bottle with a similar, screw-on, safety cap. Safety-seal beneath cap is intact. Bottle is approximately 4 cm. in diameter and 7.5 cm. in height.

Labeling: Commercially-printed, rectangular, paper, stick-on label. Commercially-printed product insert is inside bottle.

Code: " Control No.: 70811A1 " and " Exp. Date: OCT 09 " printed on each bottle label.

Product: Round, biconvex, solid, white tablet. Tablet is unmarked and unscored on one side. Opposite side is 1/2-scored with markings "B" and "146". Tablet is approximately 7.5 mm in diameter.

Analysis: Identification, Dissolution, and Content Uniformity.

Method: USP 30 - NF 25, p. 1943.

Results: See general continuation sheet page 2.

11. RESERVE SAMPLE

Original plastic bag containing one open and one intact product bottle. Bag is officially sealed " 454866 6/2/08 Valentino Fiorella Analyst". Open bottle is additionally identified " 454866 VF 2/27/08 " and contains 77 tablets. Sample returned to the sample custodian.

12.a. ANALYST SIGNATURE (Broke Seal ☒)	13. WORK-SHEET CHECK	a. BY
Valentino Fiorella		S. Matthew
b.		b. DATE 6/5/08
c.		14. DATE REPORTED 6/5/08

FORM FDA 431 (5/84) PREVIOUS EDITION IS OBSOLETE

ATTACHMENTS : A (pp. 1 - 20), B

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VF 6/2/08

GENERAL CONTINUATION SHEET	PRODUCT: Digoxin Tablets (0.25 mg)	SAMPLE NO.: 454866

RESULTS:

Identification

The retention time of the major peak in the chromatogram of the *sample preparation* corresponds to that in the chromatogram of the *standard preparation*. Complies

Content Uniformity

(See computer printout pages 6 - 7 for complete results)

Range: 94.0 % to 100.6 %; Average (X): 97.7 %;

RSD: 2.6 %; s: 2.57

Acceptance Value (AV) = 7.0 %

(Limit: AV ≤ 15.0 % unless otherwise specified in the individual monograph)

Dissolution

(See least squares line fitting pages 11 - 12 for complete results)

Range: 93.7 % to 100.4 % ; Avg.: 97.4 %

(Limit: Each unit is NLT Q+5% (Q=80%) for 6 units tested (Stage 1))

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DIGOXIN TABLETS
(USP 30-NF 25, p.1943)

Reference Std:
USP Digoxin RS # 1200000-05, Lot O0B096, dried in vacuum at 105°C for 1 hour prior to use. For quantitative applications, use a value of 0.961 mg of digoxin per mg on the dried basis.

Reagents: Fisher Scientific Acetonitrile, Lot 073938 (Rec'd 11/1/07)
Sigma Digoxigenin, Lot No. 016K3777 (Rec'd 2/6/08)

Filter: PALL Life Sciences Acrodisc 25 mm Syringe Filter with 0.45 um Nylon Membrane, Lot A10529577

Identification

The retention time of the major peak in the chromatogram of the *sample preparation* corresponds to that in the chromatogram of the *standard preparation*. Complies

Content Uniformity

Mobile Phase: Water/Acetonitrile (74/26)

System Suitability Solution
(Balance: Cahn C-31 Microbalance, FDA No. 5004472 - QA by G.Lehr on 1/14/08)

4.025 mg USP Digoxin RS + 4.122 mg Digoxigenin

----> 100.0 ml Diluted Alcohol

Standard Solution 1 (CCV)
(Balance: Cahn C-31 Microbalance, FDA No. 5004472 - QA by G.Lehr on 1/14/08)

2.522 mg USP Digoxin RS ----> 100.0 ml Diluted Alcohol

Standard Solution 2 (ICV/Check Std.)
(Balance: Cahn C-31 Microbalance, FDA No. 5004472 - QA by G.Lehr on 1/14/08)

2.505 mg USP Digoxin RS ----> 100.0 ml Diluted Alcohol

Sample Solution
For each of 10 tablets tested:

1 tablet(0.25 mg) ----> 10.0 ml Diluted Alcohol ----> Filter

GENERAL CONTINUATION SHEET	PRODUCT	SAMPLE NO.
	Digoxin Tablets (0.25 mg)	454866

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Valentino Fiorelli	113	PAGE 3 OF 12 PAGES

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Content Uniformity

Chromatographic System

Resolution (R)
(See page 2 ,Attachment A)

$R = \frac{2(t2 - t1)}{w1 + w2} =$ 20.5 [Limit: R is NLT 4.0]

Theoretical Plates (N)
(See page 3 ,Attachment A)

$N = 16(t/w)^2 =$ 6310 [Limit: N is NLT 1200]

Tailing Factor (T)
(See page 3 ,Attachment A)

$T = [W_{0.05}/2f] =$ 1.1 [Limit: T is NMT 2.0]

Relative Std. Deviation (RSD)
(See computer calculation, page 5)

RSD = 0.17 % [Limit: RSD is NMT 2.0%]

Standard 2 Calculation (ICV/Check Std.)
(See pp. 3 - 8 ,Attachment A for chromatograms)

$$\% \text{ Digoxin} = \frac{\text{Area Std.2}}{\text{Area Std.1}} \times \frac{\text{Std 1 Wt.}}{\text{Std 1 Dilution}} \times \frac{\text{Std 2 Dilution}}{\text{Std 2 Wt.}} \times 100$$

Area Std.1 = Avg.area of 5 std. injections. (See computer calculation, p. 5)
Std.Wt.1 = (2.522 mg)(0.961) = 2.424 mg
Std.Wt.2 = (2.505 mg)(0.961) = 2.407 mg

$$\% \text{ Digoxin} = \frac{1344686}{1366405} \times \frac{2.424 \text{ mg}}{100.0 \text{ ml}} \times \frac{100.0 \text{ ml}}{2.407 \text{ mg}} \times 100 = 99.1 \%$$

GENERAL CONTINUATION SHEET	PRODUCT	SAMPLE NO.
	Digoxin Tablets (0.25 mg)	454866

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Standard 1 Calculation (CCV)
(See pp. 3 - 7 and page 20, Attachment A for chromatograms)

$$\% \text{ Digoxin} = \frac{\text{Area Std.1(7)}}{\text{Area Std.1}} \times \frac{\text{Std 1 Wt.}}{\text{Std 1 Dilution}} \times \frac{\text{Std 1 Dilution}}{\text{Std 1 Wt.}} \times 100$$

Area Std.1 = Avg. area of 5 std. injections. (See computer calculation, p. 5)
Area Std.1(7) = Area of Std.1, Injection 7. (See page 20, Attachment A)
Std.Wt.1 = (2.522 mg)(0.961) = 2.424 mg

$$\% \text{ Digoxin} = \frac{1367356}{1366405} \times \frac{2.424 \text{ mg}}{100.0 \text{ ml}} \times \frac{100.0 \text{ ml}}{2.424 \text{ mg}} \times 100 = 100.1\%$$

Calculations
(See computer printout pages 6 - 7 for complete results and pages 9-13 & 15-19, Attachment A for chromatograms)

Area Std.1 = Avg.area of 5 std. injections. (See computer calculation, p. 5)
Std.Wt.1 = (2.522 mg)(0.961) = 2.424 mg

If X < 98.5%, then M = 98.5%

Range: 94.0 % to 100.6 %; Average(X): 97.7 %; RSD: 2.6 %; s: 2.57

Acceptance Value(AV) = M - X + ks

AV = 98.5% - 97.7 + (2.4)(2.57) = 6.97 %

(Limit: AV ≤ 15.0 % unless otherwise specified in the individual monograph)

Statistical Analysis of Data:

Standard Solution 1 (CCV) 03/11/2008

Relative STD Deviation	**0.17 %**		
Standard Deviation	2344.76071		
Average (mean)	**1366404.6**		
Number of entries	5		
Range	1362386	To	1368470

Data Entered:

1362386
1367309
1366606
1367252
1368470

Analyst(s) Valentina Fiorelli | Analyst No. 113 | Page 5 of 12 Pages

General Information Sheet | Product: Digoxin Tablets (0.25 mg) | Sample No. 454866

Content Uniformity

03/12/2008

No. of Units Examined	10
Standard Weight	2.424 mg.
Standard Dilution	100
Sample Dilution	10

Data Entered:

Unit #1	1417304	STD #1	1366405
Unit #2	1404370	Blank	0
Unit #3	1324637		
Unit #4	1391323		
Unit #5	1381563		
Unit #6	1342615		
Unit #7	1409901		
Unit #8	1350277		
Unit #9	1413012		
Unit #10	1330349		

CONTENT UNIFORMITY RESULTS:

	FOUND (mg/tablet)	DECLARED	% of DECLARED
UNIT #1	0.251	0.25 mg/tablet	100.6
UNIT #2	0.249		99.7
UNIT #3	0.235		94.0
UNIT #4	0.247		98.7
UNIT #5	0.245		98.0
UNIT #6	0.238		95.3
UNIT #7	0.250		100.0
UNIT #8	0.240		95.8
UNIT #9	0.251		100.3
UNIT #10	0.236		94.4
AVG.	**0.244**		**97.7**

OFFICIAL LIMITS:	90.0 %	TO	105.0 %		
No. of Units Examined	10				
RANGE	**94.0 %**	**TO**	**100.6 %**	**of Declared**	
UNITS >=85 BUT <=115 % of Avg. Limit				:	10
UNITS >=75 BUT <85 OR >115 BUT <=125 % of Avg. Limit				:	0
UNITS <75 OR >125 % of Avg. Limit				:	0
REL. STD. DEV. :	**2.6** LIMIT <= 6.0%				

mg/unit = (R_spl * std_wt * spl_dil) / (R_std * std_dil * 1 unit)

Analyst(s) Valentino Fiorelli | Analyst No. 113 | Page 6 of 12 Pages

Statistical Analysis of Data:

Content Uniformity
Standard Deviation

03/12/2008

Relative STD Deviation	2.63 %		
Standard Deviation	**2.57**		
Average (mean)	97.68		
Number of entries	10		
Range	94	To	100.6

Data Entered:

100.6
99.7
94
98.7
98
95.3
100
95.8
100.3
94.4

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	Digoxin Tablets (0.25 mg)	454866

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Dissolution

Medium: 0.1N HCl, 500 ml (37.0°C ± 0.5°C)
Apparatus 1: 120 rpm
Time: 60 minutes
Instrument: Distek Dissolution Apparatus #1, FDA No. 1218
(QA by R.Muzeni on 4/9/08)
Instrument: Shimadzu Fluorescence Spectrophotometer, FDA# 5004459
(QA by V.Fiorella on 1/11/08)
Reagents: Sigma L-Ascorbic Acid, Lot 10K0256 (Rec'd before 4/10/06)
Sigma-Aldrich 30% H_2O_2, Batch# 04824AH (Rec'd 4/3/08)
Burdick & Jackson Methanol, Lot CU893 (Rec'd 12/20/07)
Fisher Scientific HCl, Lot 068102 (Rec'd 5/4/07)
Filter: PALL Life Sciences GHP Acrodisc 25 mm Syringe Filter with 0.45 um GHP Membrane, Lot A10646119

Ascorbic acid-Methanol Solution

(Mettler Toledo AX205, FDA No. 5099471 - QA by A.Stewart on 4/3/08)

204.0 mg Ascorbic acid ----> 100.0 ml MeOH

Hydrogen peroxide-Methanol Solution

Stock Solution: 2.0 ml 30% H_2O_2 ---> 100.0 ml MeOH (Refrigerate)

Working Solution: 2.0 ml Stock ---> 100.0 ml MeOH

Standard Solutions

(Cahn C-31 Microbalance, FDA No. 5004472 - QA by D.Dai on 4/14/08)

Stock Solution

25.013 mg USP Digoxin RS ---> 500.0 ml Dilute Alcohol (4 in 5)

10.0 ml
----------> 100.0 ml Dilute Alcohol (4 in 5) [0.005 mg/ml]

GENERAL CONTINUATION SHEET	PRODUCT	SAMPLE NO.
	Digoxin Tablets (0.25 mg)	454866

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Working Standard Solutions

Standard Solution	ml Stock Solution	ml Dissolution Medium	Final Concentration (mg/ml)
20%	1.0	50.0	0.00010
40%	2.0	50.0	0.00020
60%	3.0	50.0	0.00030
80%	4.0	50.0	0.00040
100%	5.0	50.0	0.00050

Test Solution (6 tablets tested; 0.25 mg/tablet)

1 tablet ---> 0.1N HCl, 500 ml ---> Filter [0.0005 mg/ml]

Procedure

Test Prep.: 1.0 ml Test Solution (Prepared in duplicate)
+ 1.0 ml Ascorbic acid-Methanol Solution
+ 5.0 ml HCl
+ 1.0 ml Hydrogen peroxide-Methanol Solution

----> Glass-stoppered flask

Std. Preps.: 1.0 ml of each Working Std. Solution
+ 1.0 ml Ascorbic acid-Methanol Solution
+ 5.0 ml HCl
+ 1.0 ml Hydrogen peroxide-Methanol Solution

----> Glass-stoppered flask

Blank Prep.: 1.0 ml Dissolution Medium
+ 1.0 ml Ascorbic acid-Methanol Solution
+ 5.0 ml HCl
+ 1.0 ml Hydrogen peroxide-Methanol Solution

----> Glass-stoppered flask

GENERAL CONTINUATION SHEET	PRODUCT	SAMPLE NO.
	Digoxin Tablets (0.25 mg)	454866

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Procedure

After 2 hours (FDA Timer# 1678 - QA by A.Vargas on 1/18/08), measure the fluorescence of each preparation at an emission wavelength of about 485 nm and an excitation wavelength of about 372 nm correcting each reading for the blank.

Plot a standard curve of Fluorescence vs. % Dissolution.

Determine the % dissolution of digoxin for each Test Solution from the graph.

Results

See least squares line fitting pages 11 - 12 for complete results and Attachment B for spectra.

Tablet	Avg. % Dissolution
1	98.36
2	97.45
3	98.10
4	100.41
5	95.77
6	93.69
Avg. (6 Tablets)	97.41

[Limit: Each unit is NLT Q + 5% (Q=80%) for 6 units tested (Stage 1)]

Least Squares Line Fitting

05/30/2008

The Line Fitting used is Y = mX + b

with m = 0.03896
and b = 0.0204
Correlation Cofficient = 0.993365369

Data Entered:

	X	y	LSLF y	% Deviation
20 % Std.	20	0.761	0.7996	4.827
40 % Std.	40	1.489	1.5788	5.688
60 % Std.	60	2.61	2.358	10.687
80 % Std.	80	3.057	3.1372	2.556
100 % Std.	100	3.873	3.9164	1.108

Extrapolated Data:

	X	AVG	Y
Tablet 1-Test 1	96.58		3.783
Tablet 1-Test 2	100.14	98.36	3.922
Tablet 2-Test 1	96.73		3.789
Tablet 2-Test 2	98.17	97.45	3.845
Tablet 3-Test 1	103.71		4.061
Tablet 3-Test 2	93.88	98.80	3.678

Least Squares Line Fitting

05/30/2008

The Line Fitting used is Y = mX + b

with m = 0.03896

and b = 0.0204

Correlation Cofficient = 0.993365369

Data Entered:

	X	y	LSLF y	% Deviation
20 % Std.	20	0.761	0.7996	4.827
40 % Std.	40	1.489	1.5788	5.688
60 % Std.	60	2.61	2.358	10.687
80 % Std.	80	3.057	3.1372	2.556
100 % Std.	100	3.873	3.9164	1.108

Extrapolated Data:

	X	AVG	Y
Tablet 4-Test 1	100.55		3.938
Tablet 4-Test 2	100.27	100.41	3.927
Tablet 5-Test 1	96.29		3.772
Tablet 5-Test 2	95.24	95.77	3.731
Tablet 6-Test 1	95.16		3.728
Tablet 6-Test 2	92.21	93.69	3.613

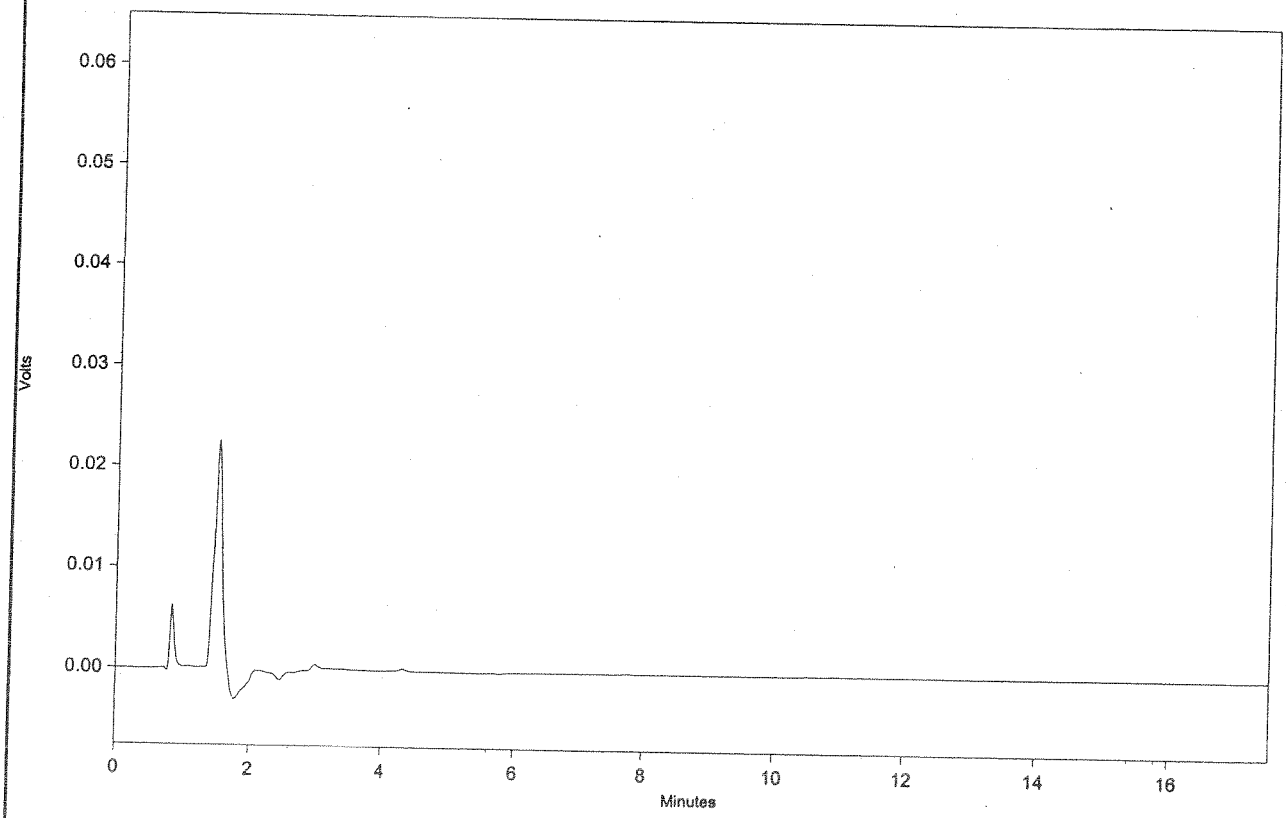
Analyst(s) Valentino Fiorillo | Analyst No. 113 | Page 12 of 12 Pages

ATTACHMENT A - Page 1 of 20 pages **Product:** Digoxin Tablets (0.25 mg) **Spl.No.** 454866

Name: Blank
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Blank-Rep2
Date: 03/11/2008 6:52:47 AM
Vial: 0
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates



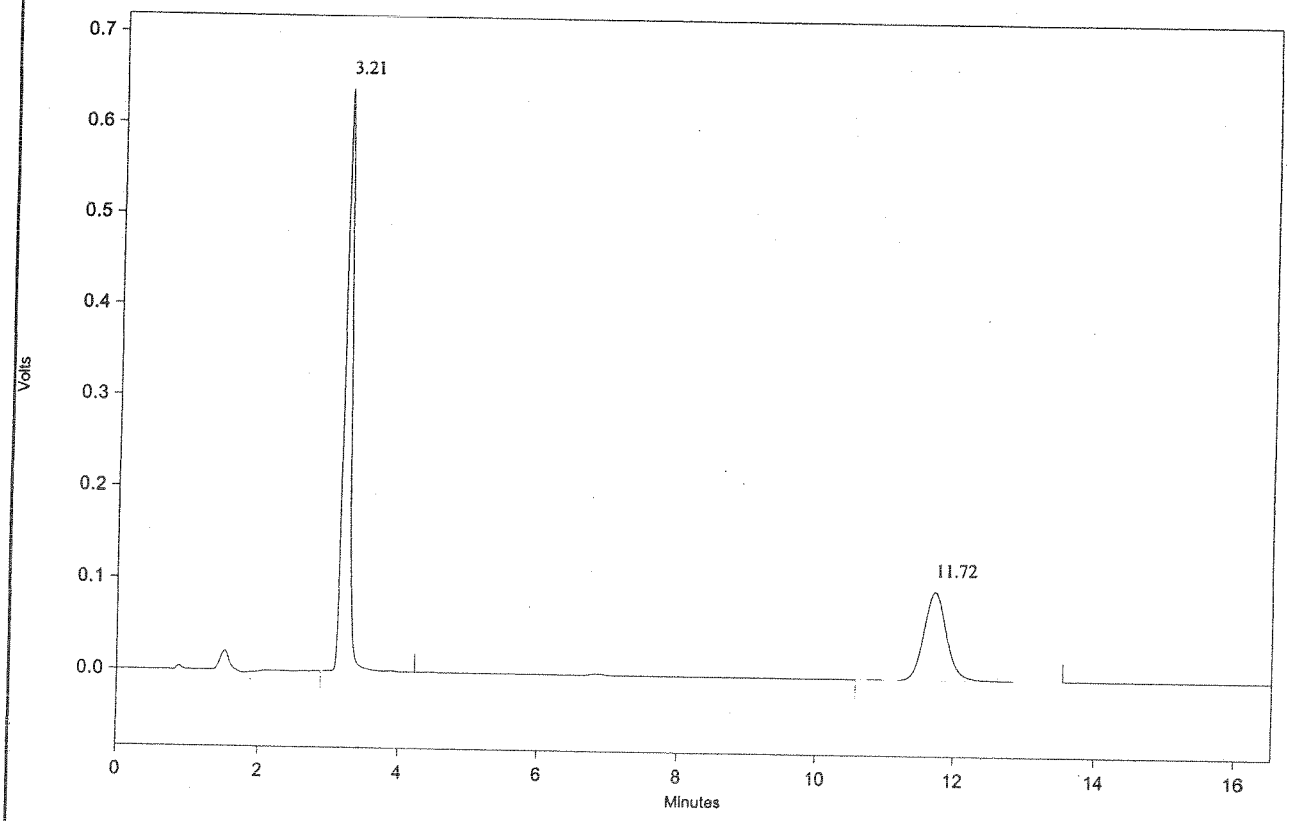
Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

ATTACHMENT A - Page 2 of 20 pages **Product:** Digoxin Tablets (0.25 mg) **Spl.No.** 454866

Name: System Suitability Solution
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\SysSuitSoln.
Date: 03/11/2008 7:11:45 AM
Vial: 1
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxigenin	3.21	4406694	638859	1.2	0.0	2980
2	Digoxin	11.72	2188974	96494	1.1	20.5	6238
Totals			6595668	735353			



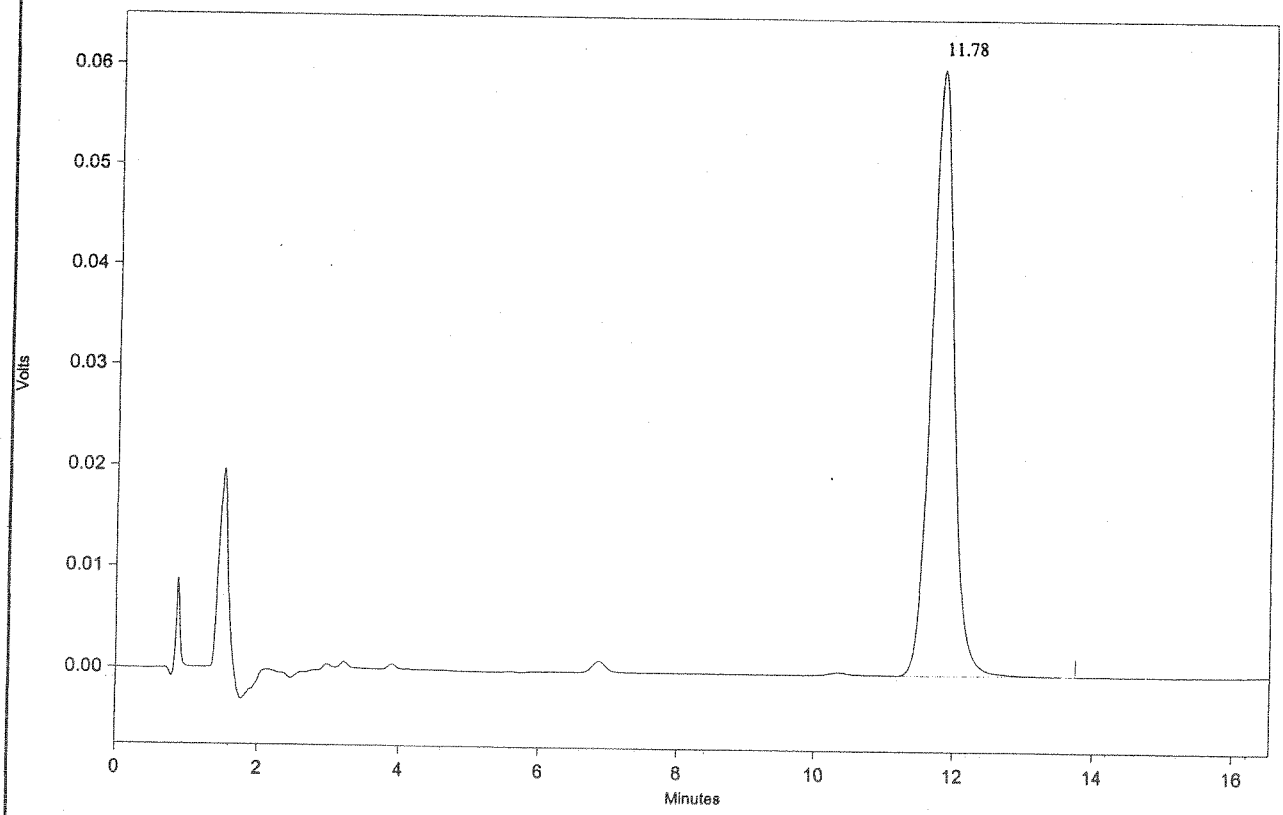
Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

ATTACHMENT A - Page 3 of 20 pages **Product:** Digoxin Tablets (0.25 mg) **Spl.No.** 454866

Name: Standard Solution 1 (CCV)
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Std.Soln-Rep1.
Date: 03/11/2008 7:34:09 AM
Vial: 2
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	11.78	1362386	60166	1.1	0.0	6310
Totals			1362386	60166			

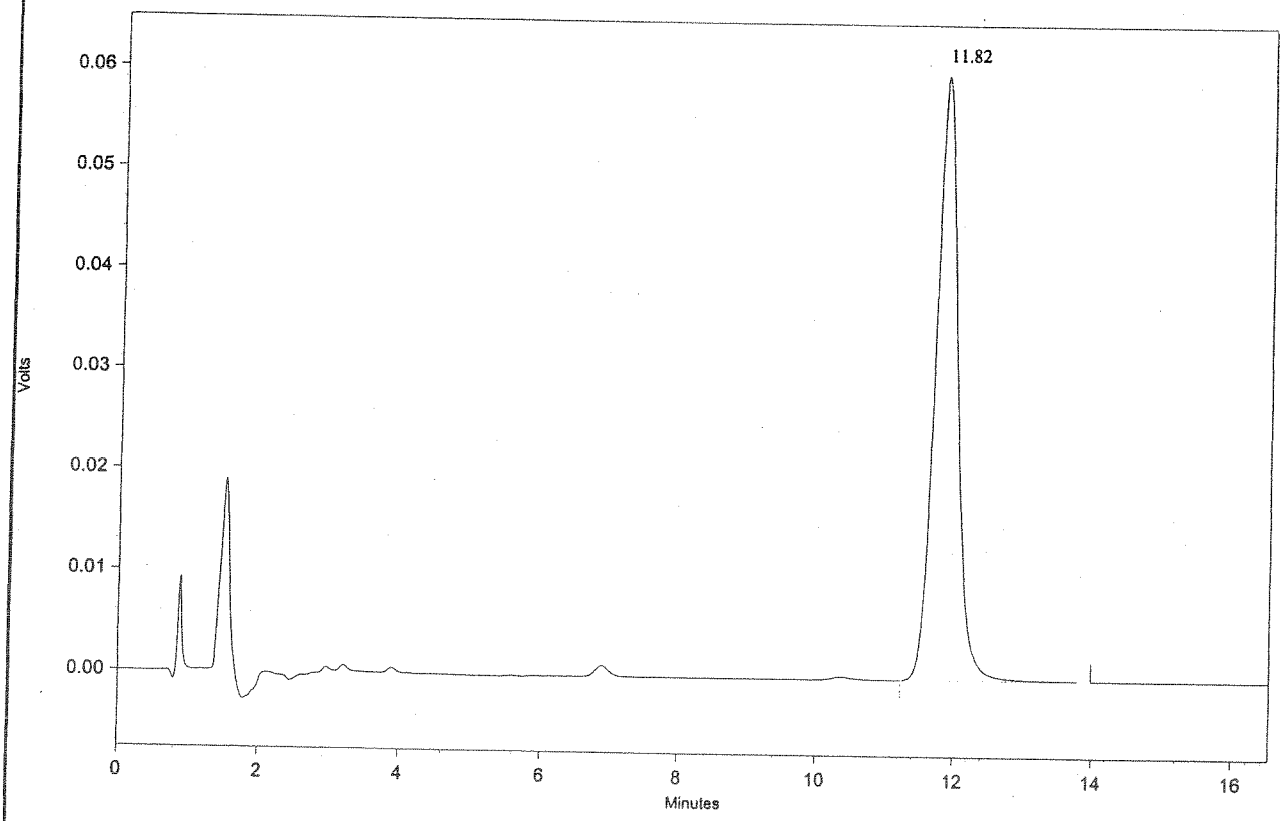


Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

Name: Standard Solution 1 (CCV)
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Std.Soln-Rep2.
Date: 03/11/2008 7:52:07 AM
Vial: 2
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	11.82	1367309	59911	1.1	0.0	6364
Totals			1367309	59911			



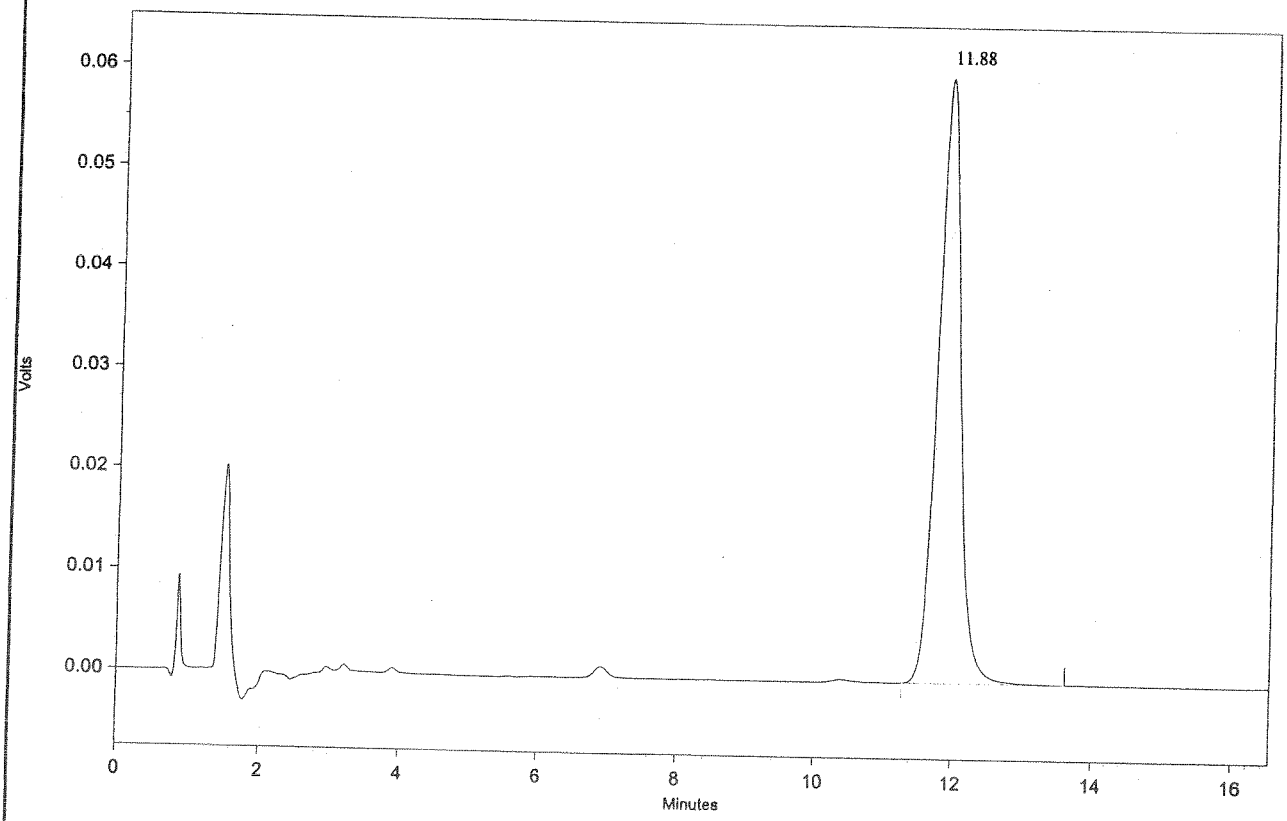
Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

ATTACHMENT A - Page 5 of 20 pages **Product:** Digoxin Tablets (0.25 mg) **Spl.No.** 454866

Name: Standard Solution 1 (CCV)
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Std.Soln-Rep3.
Date: 03/11/2008 8:10:06 AM
Vial: 2
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	11.88	1366606	59959	1.1	0.0	6307
Totals			1366606	59959			



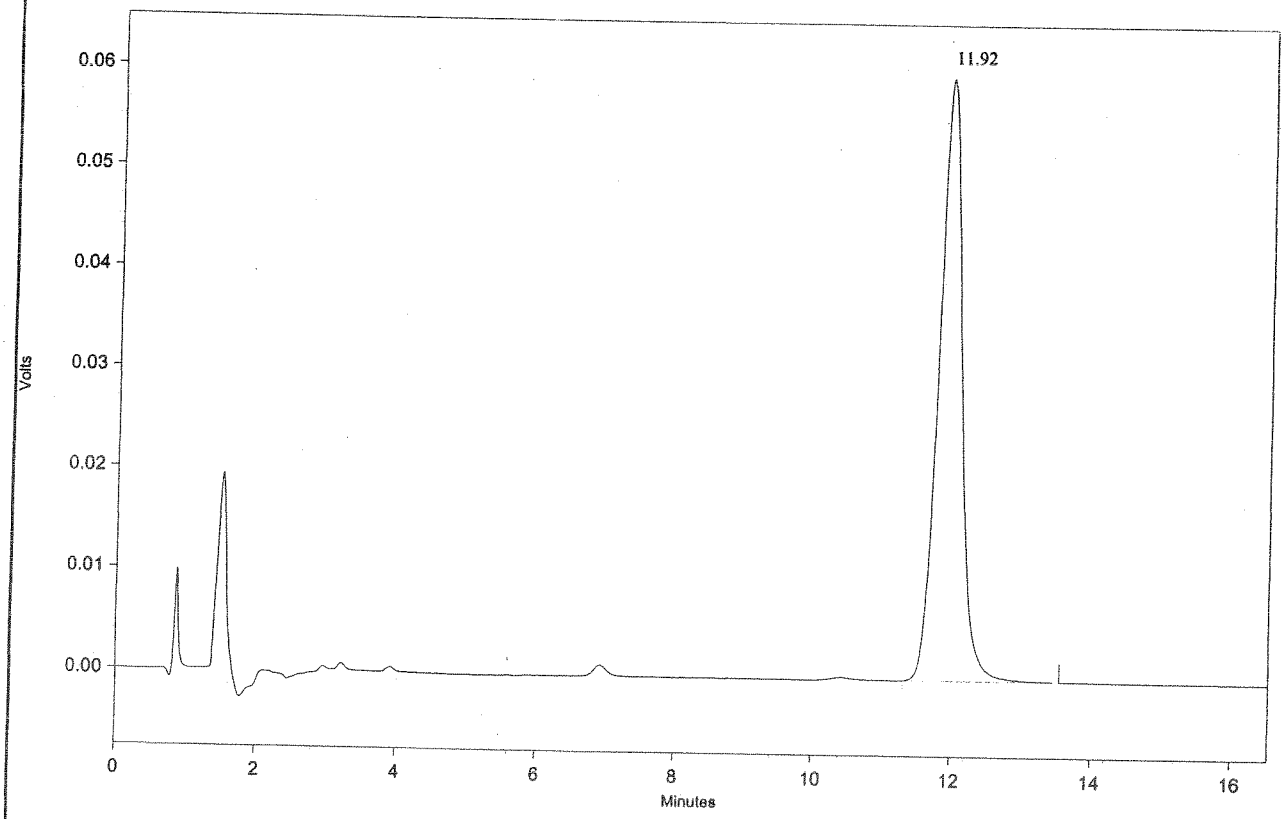
Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

ATTACHMENT A - Page 6 of 20 pages **Product:** Digoxin Tablets (0.25 mg) **Spl.No.** 454866

Name: Standard Solution 1 (CCV)
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Std.Soln-Rep4.
Date: 03/11/2008 8:28:00 AM
Vial: 2
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	11.92	1367252	59705	1.1	0.0	6341
Totals			1367252	59705			

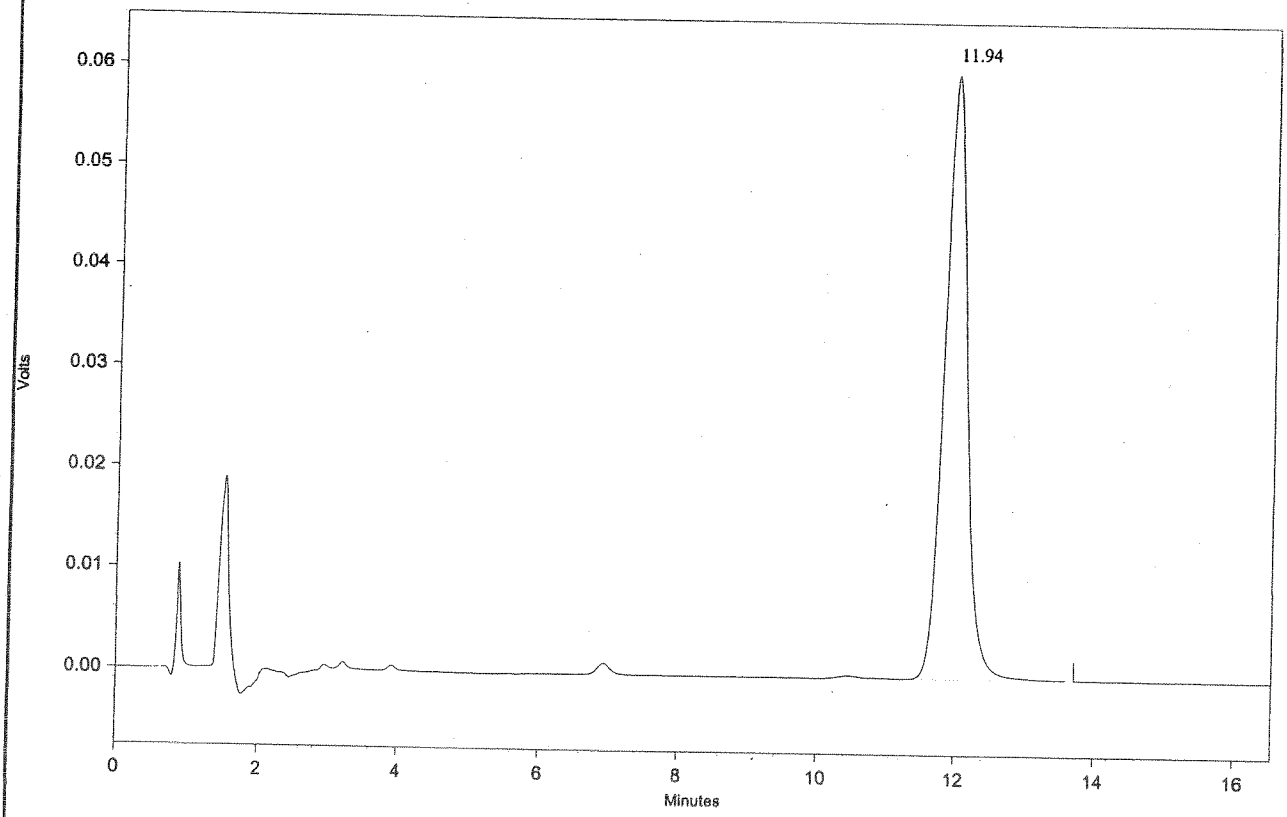


Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

Name: Standard Solution 1 (CCV)
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Std.Soln-Rep5.
Date: 03/11/2008 8:45:59 AM
Vial: 2
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	11.94	1368470	59833	1.1	0.0	6346
Totals			1368470	59833			

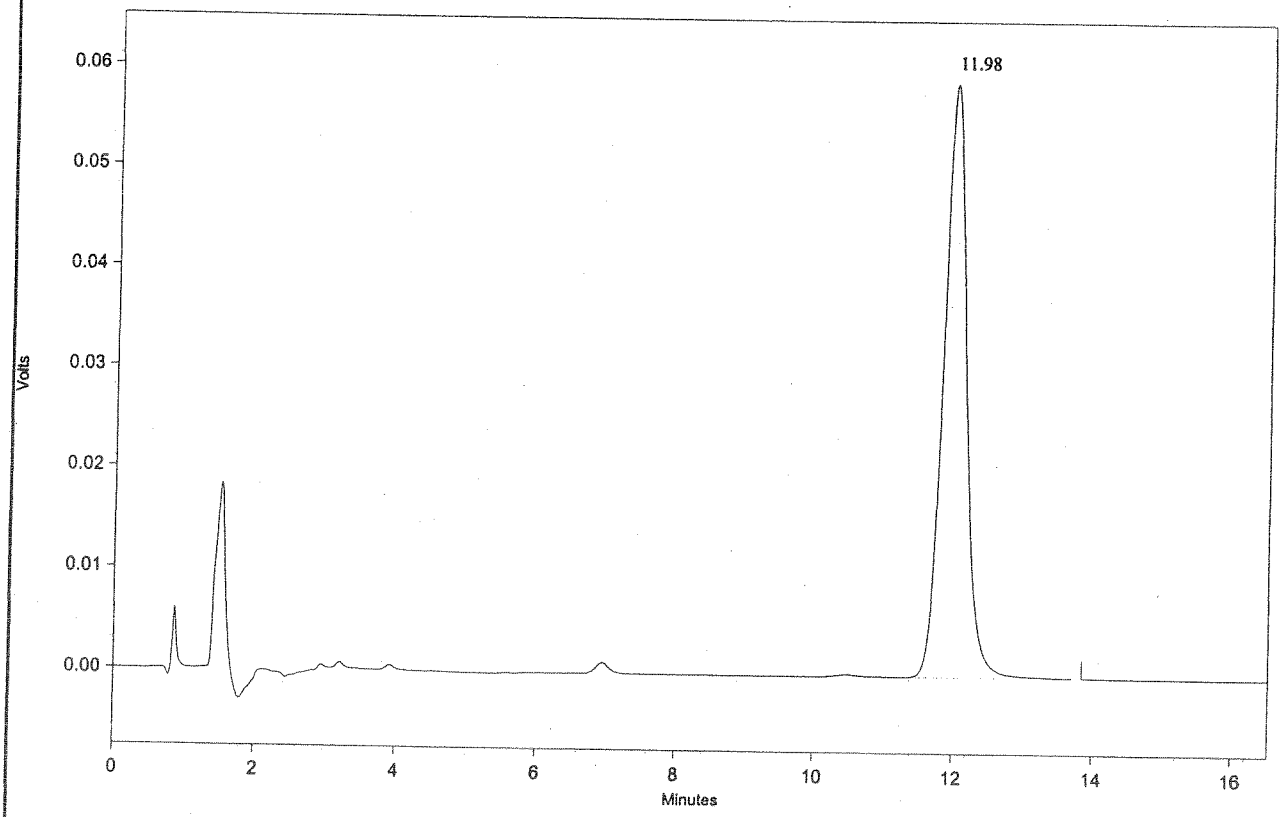


Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

Name: Standard Solution 2 (ICV)
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\CheckStd.
Date: 03/11/2008 9:03:58 AM
Vial: 3
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	11.98	1344686	58838	1.1	0.0	6259
Totals			1344686	58838			



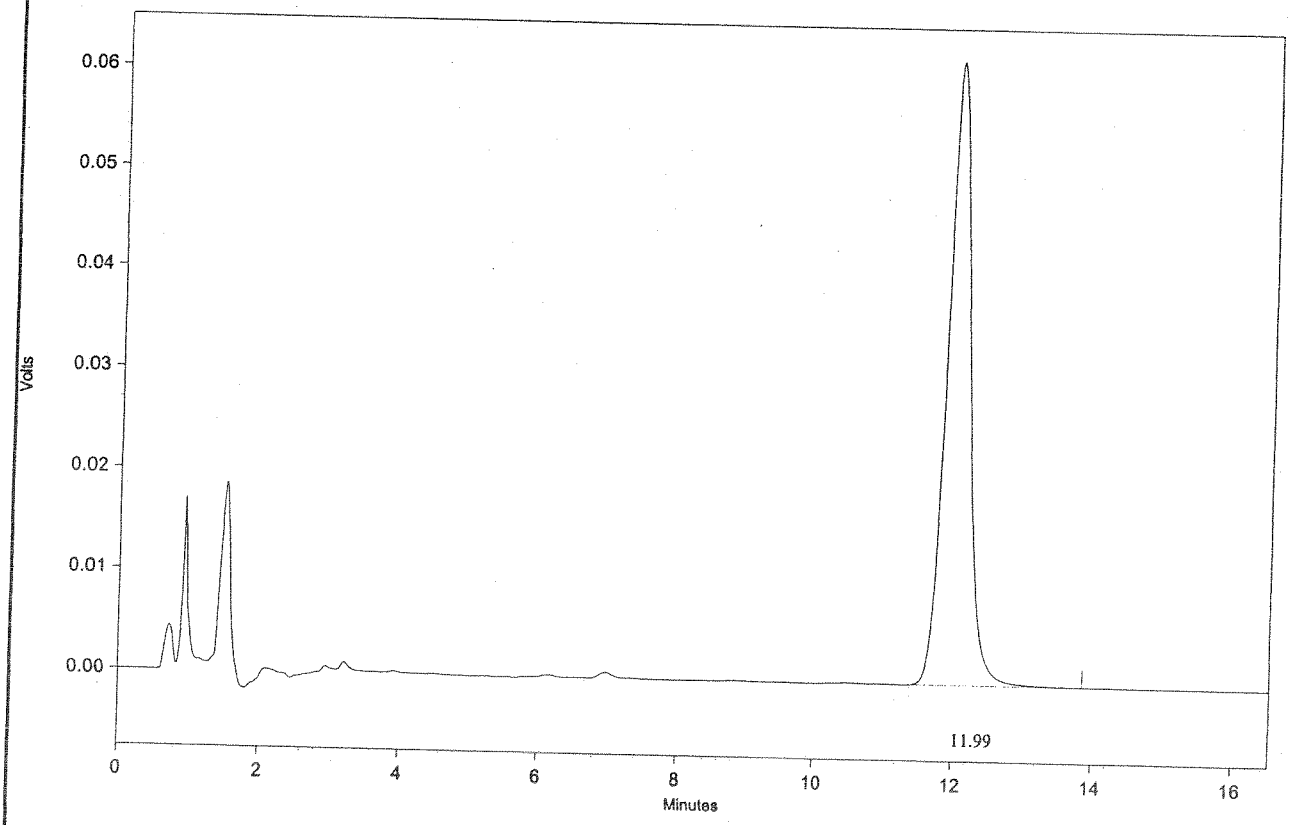
Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

 Product: Digoxin Tablets (0.25 mg) **Spl.No.** 454866

Name: Tablet 1
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Tab1
Date: 03/11/2008 9:21:56 AM
Vial: 4
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	11.99	1417304	61801	1.1	0.0	6474
Totals			1417304	61801			

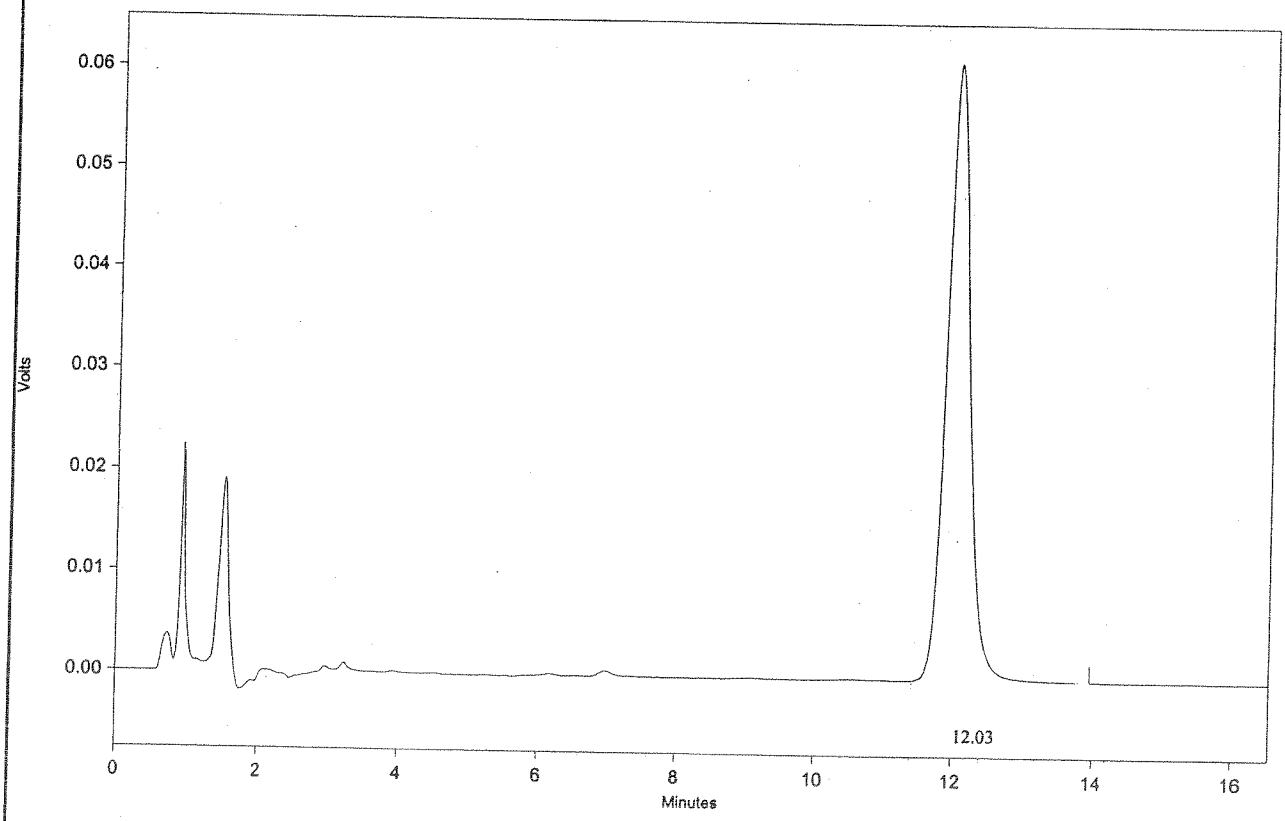


Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

Name: Tablet 2
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Tab2
Date: 03/11/2008 9:39:55 AM
Vial: 5
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	12.03	1404370	61130	1.1	0.0	6478
Totals			1404370	61130			

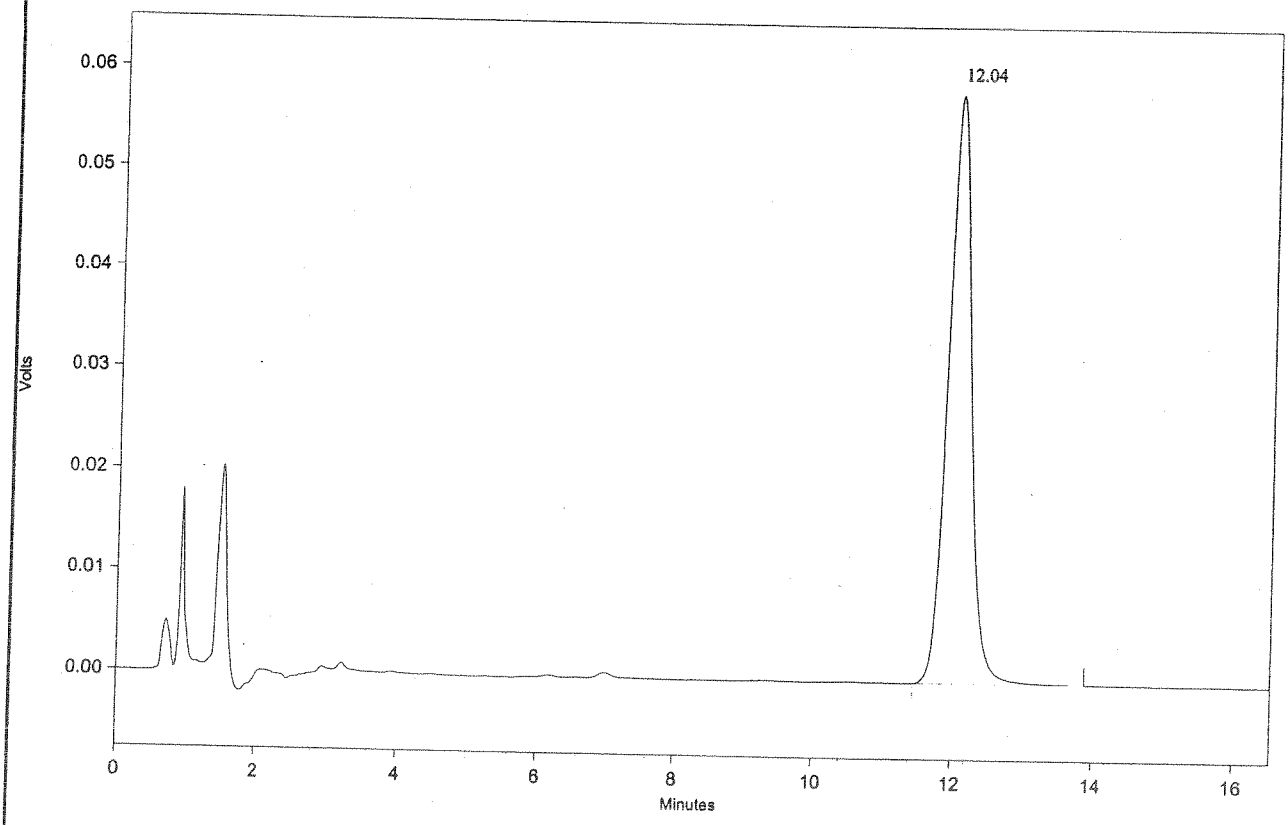


Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

Name: Tablet 3
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Tab3
Date: 03/11/2008 9:57:52 AM
Vial: 6
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	12.04	1324637	58257	1.1	0.0	6366
Totals			1324637	58257			

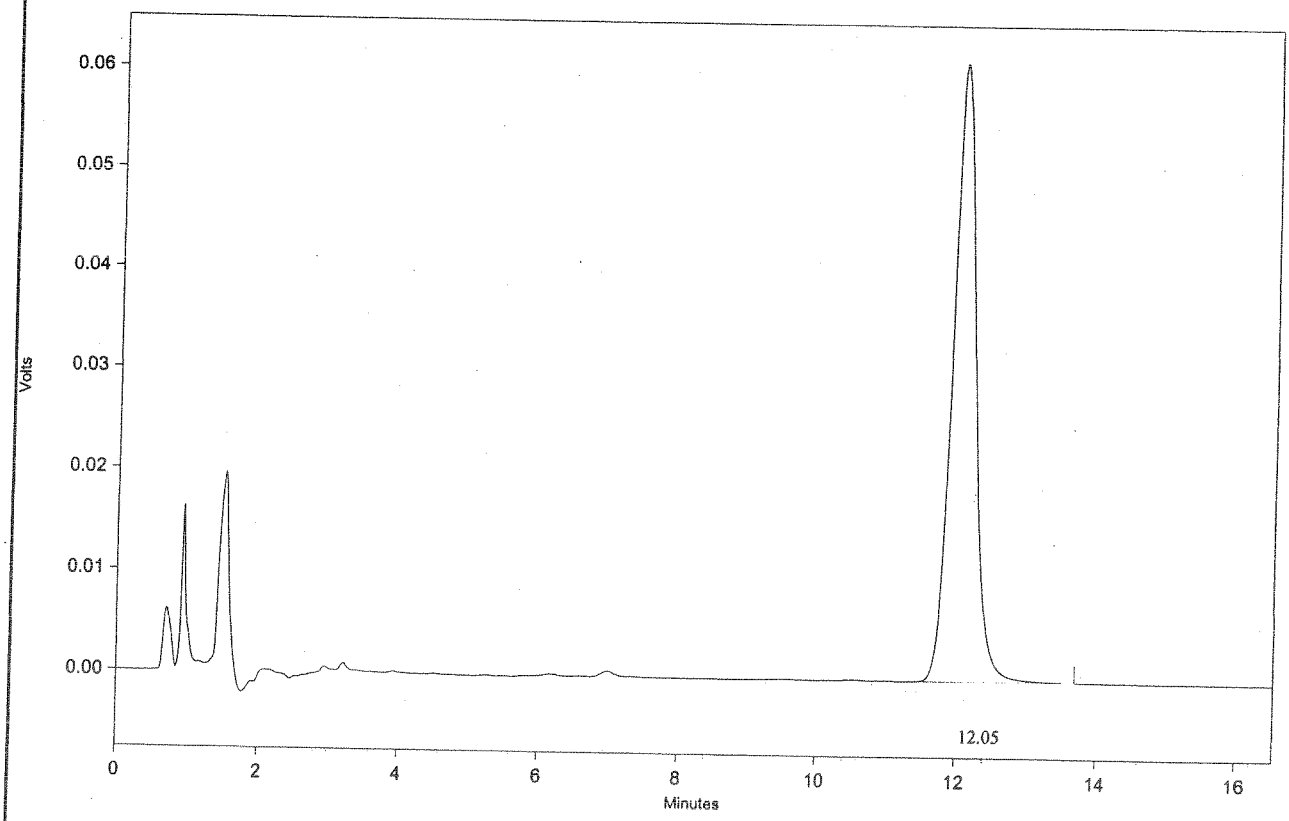


Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

Name: Tablet 4
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Tab4
Date: 03/11/2008 10:15:50 AM
Vial: 7
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	12.05	1391323	61289	1.1	0.0	6534
Totals			1391323	61289			

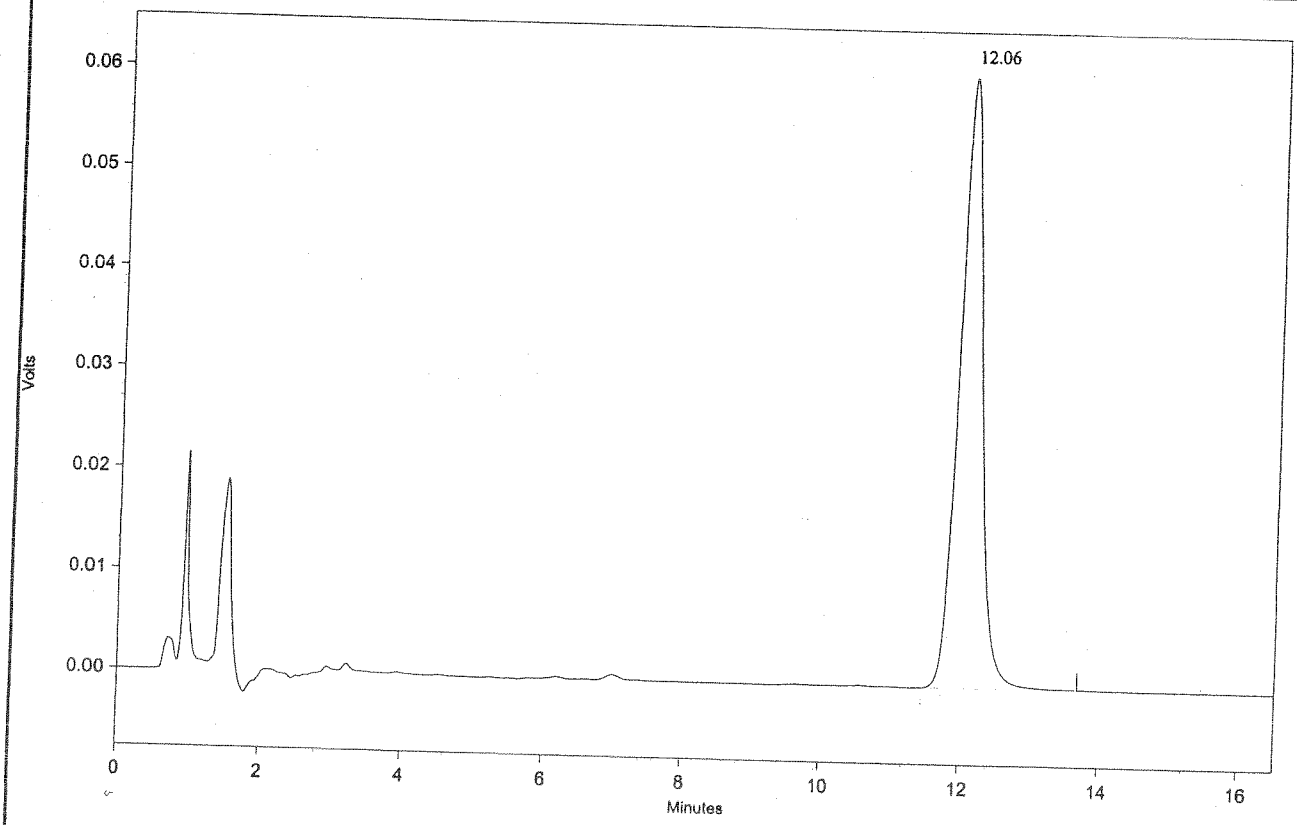


Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

Name: Tablet 5
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Tab5
Date: 03/11/2008 10:31:35 AM
Vial: 8
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	12.06	1381563	60500	1.1	0.0	6572
Totals			1381563	60500			

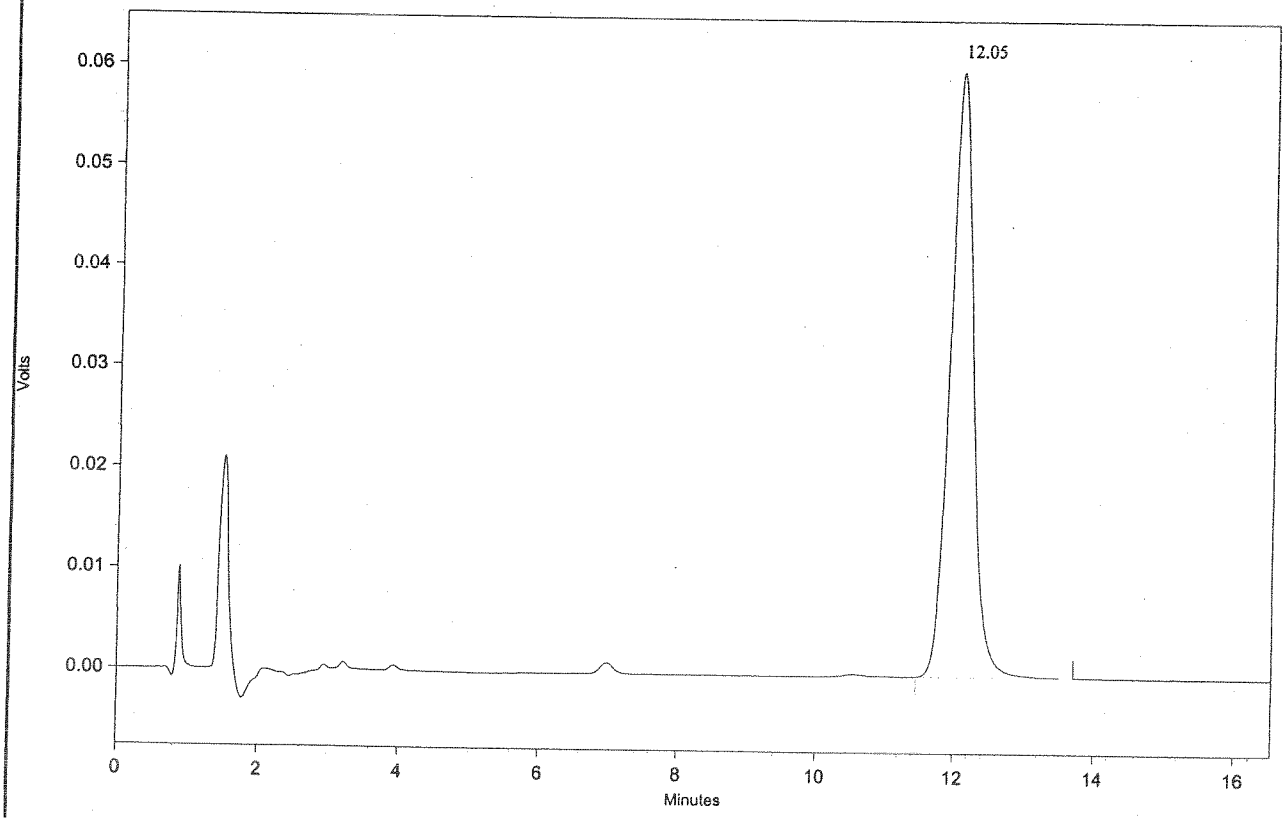


Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

Name: Standard Solution 1 (CCV)
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Std.Soln.6
Date: 03/11/2008 10:49:27 AM
Vial: 2
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	12.05	1366930	59987	1.1	0.0	6534
Totals			1366930	59987			



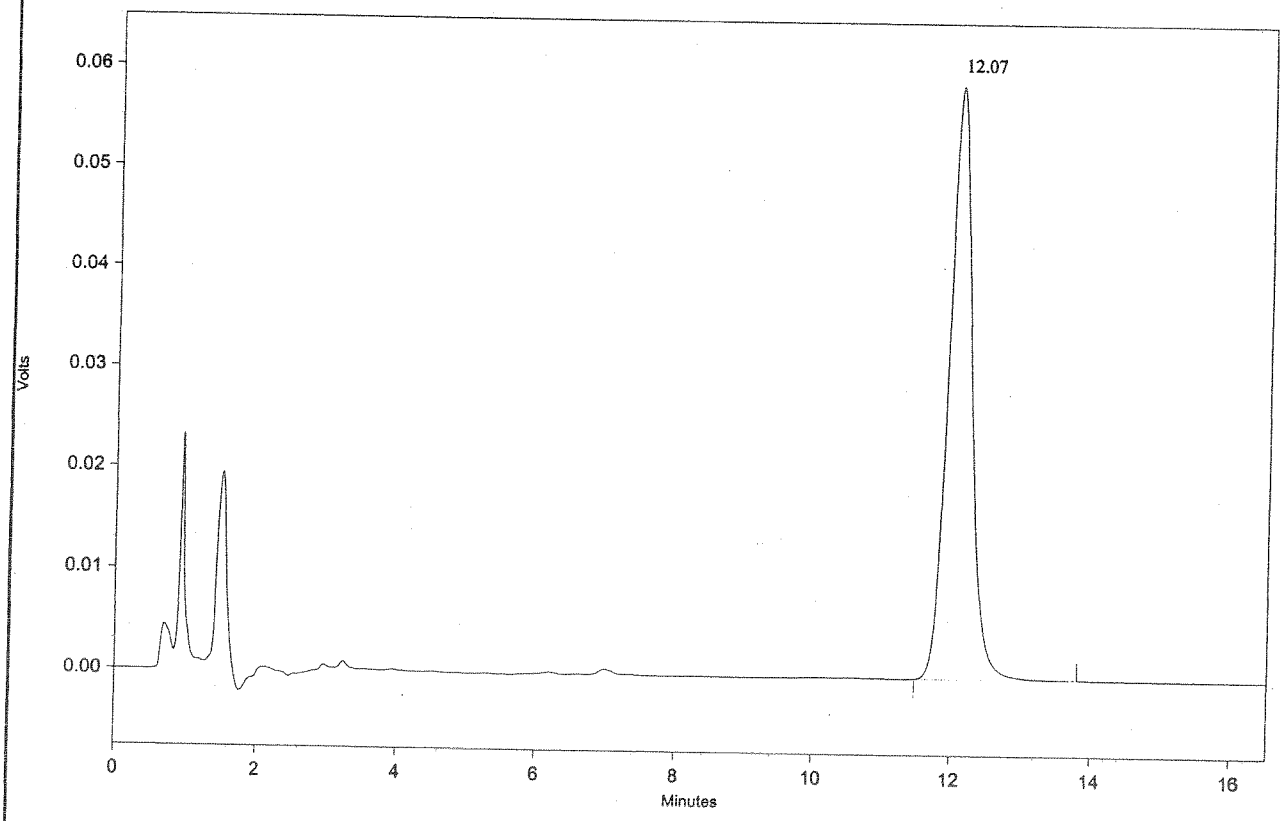
Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

ATTACHMENT A - Page 15 of 20 pages **Product:** Digoxin Tablets (0.25 mg) **Spl.No.** 454866

Name: Tablet 6
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Tab6
Date: 03/11/2008 11:07:26 AM
Vial: 9
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	12.07	1342615	58765	1.1	0.0	6353
Totals			1342615	58765			



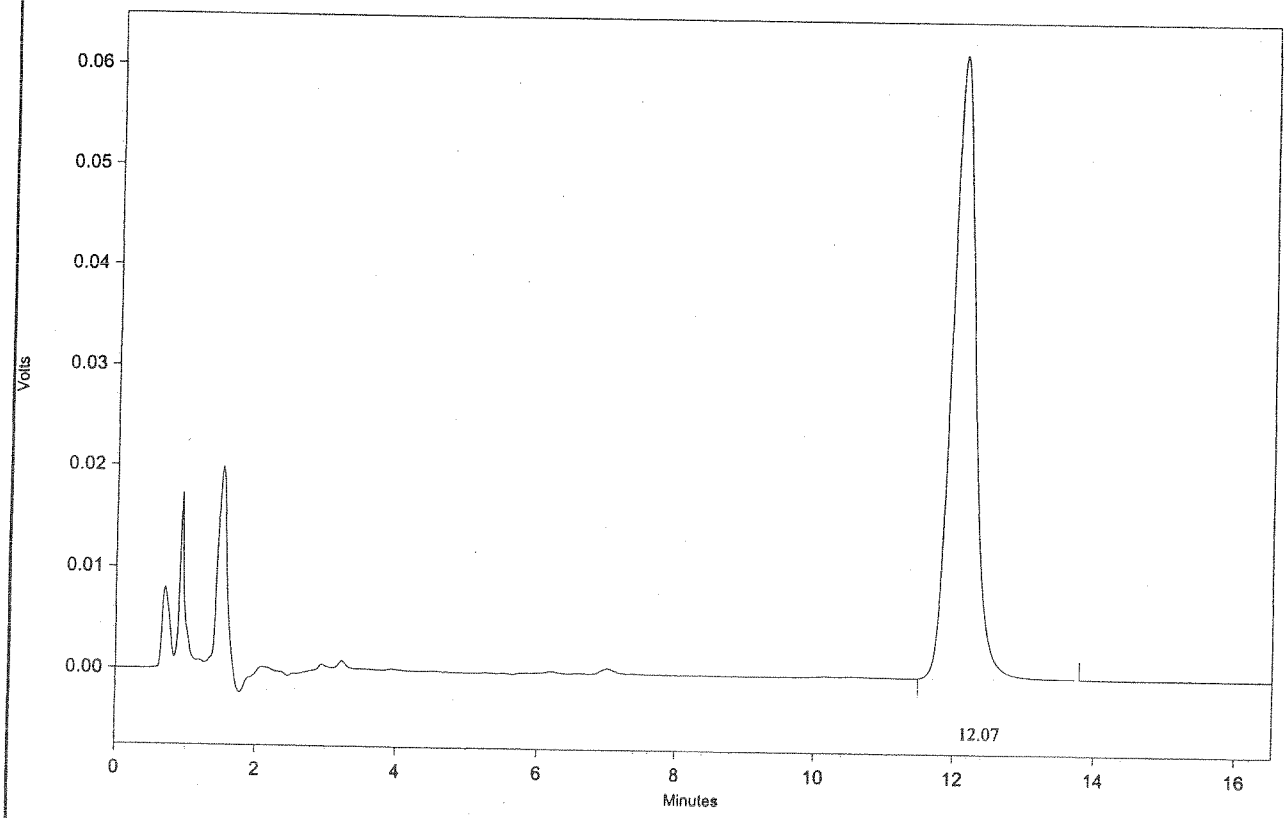
Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

 Product: Digoxin Tablets (0.25 mg) **Spl.No.** 454866

Name: Tablet 7
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Tab7
Date: 03/11/2008 11:25:18 AM
Vial: 10
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	12.07	1409901	61802	1.1	0.0	6365
Totals			1409901	61802			

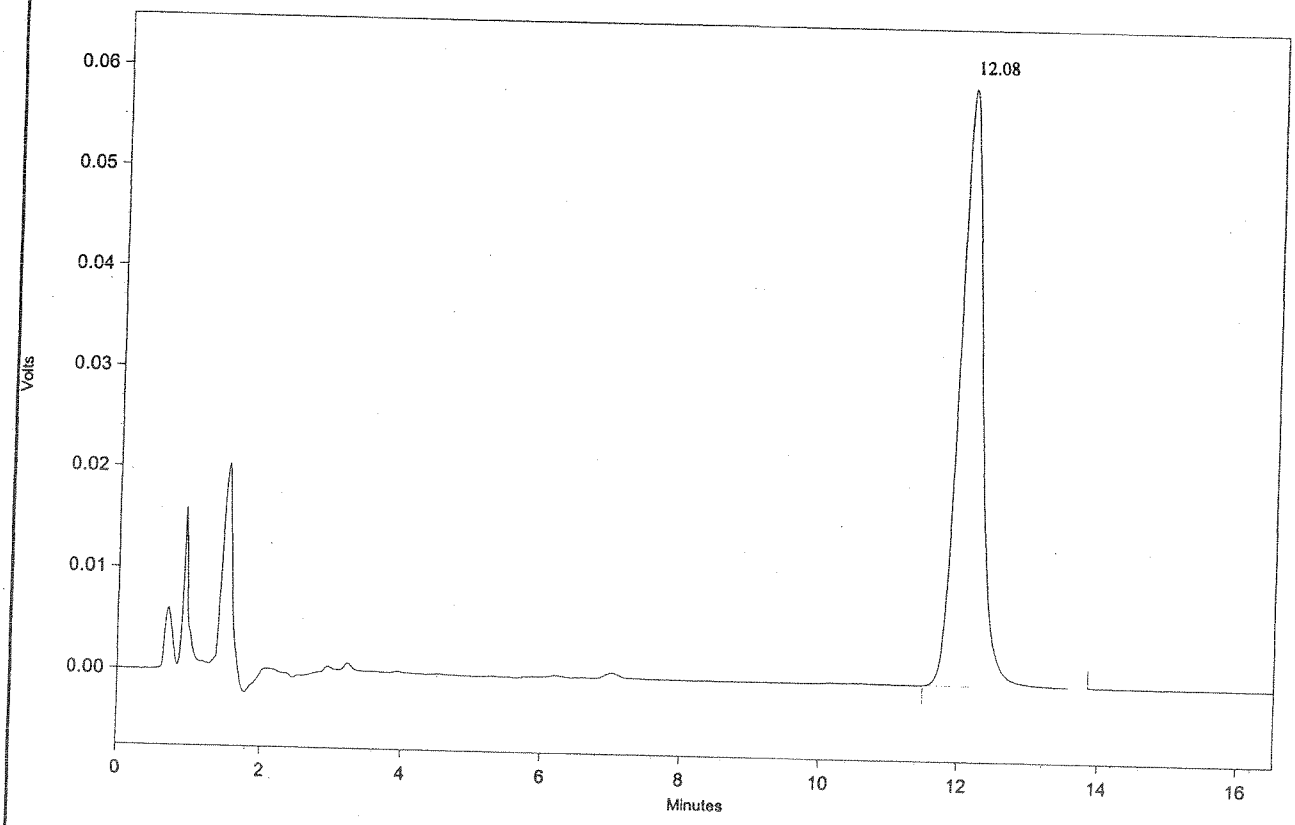


Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

Name: Tablet 8
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Tab8
Date: 03/11/2008 11:43:15 AM
Vial: 11
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	12.08	1350277	59186	1.1	0.0	6582
Totals			1350277	59186			

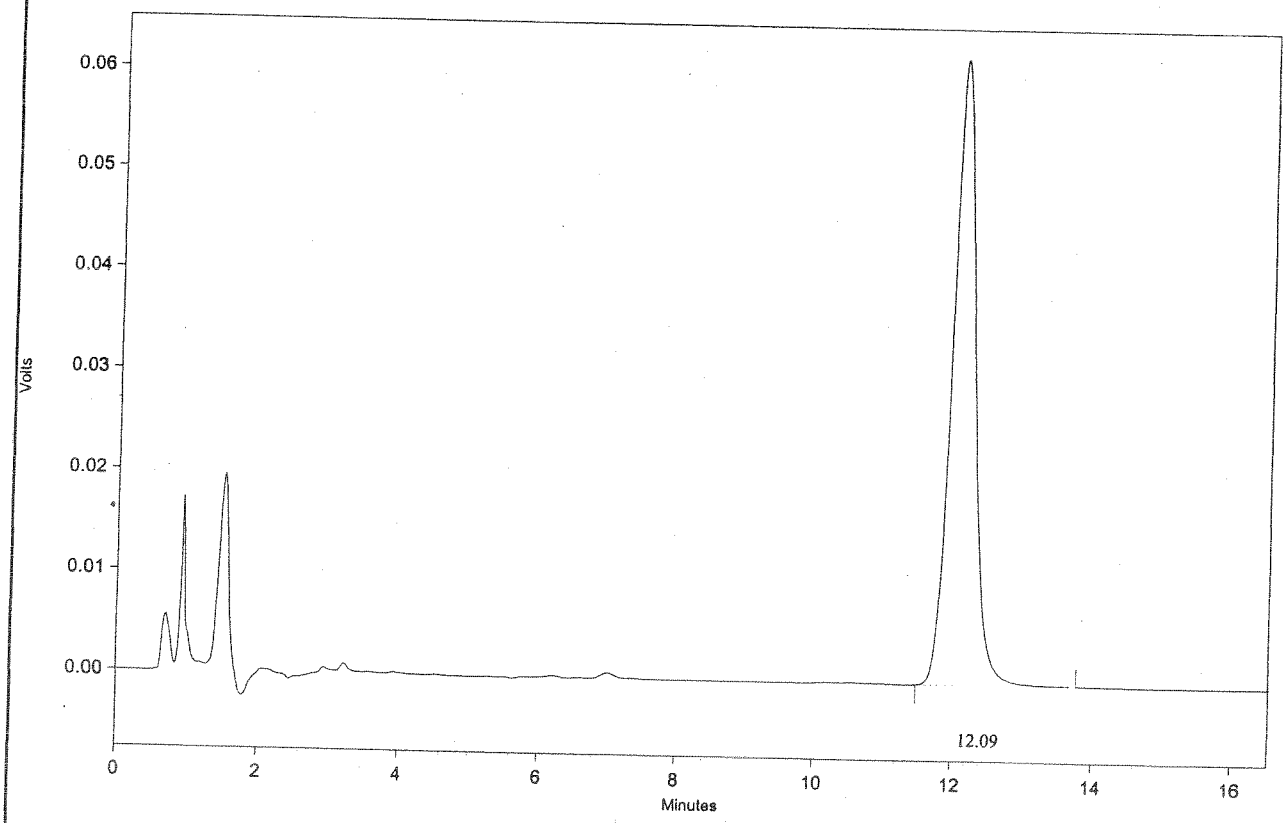


Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

Name: Tablet 9
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Tab9
Date: 03/11/2008 12:01:13 PM
Vial: 12
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	12.09	1413012	62006	1.1	0.0	6621
Totals			1413012	62006			

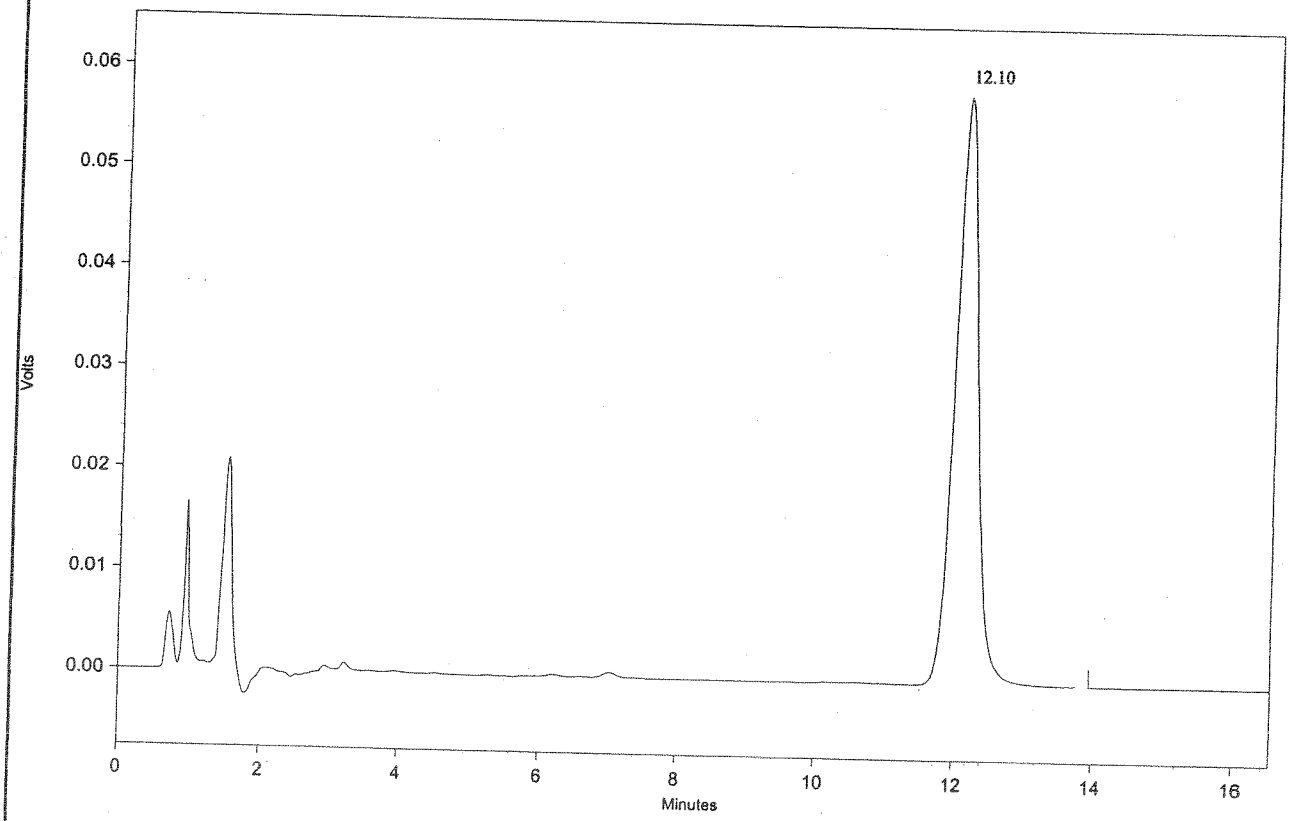


Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

Name: Tablet 10
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Tab10
Date: 03/11/2008 12:19:11 PM
Vial: 13
Injection Volume: 50 ul

Detector A
(218nm)

Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	12.10	1330349	58215	1.1	0.0	6621
Totals			1330349	58215			

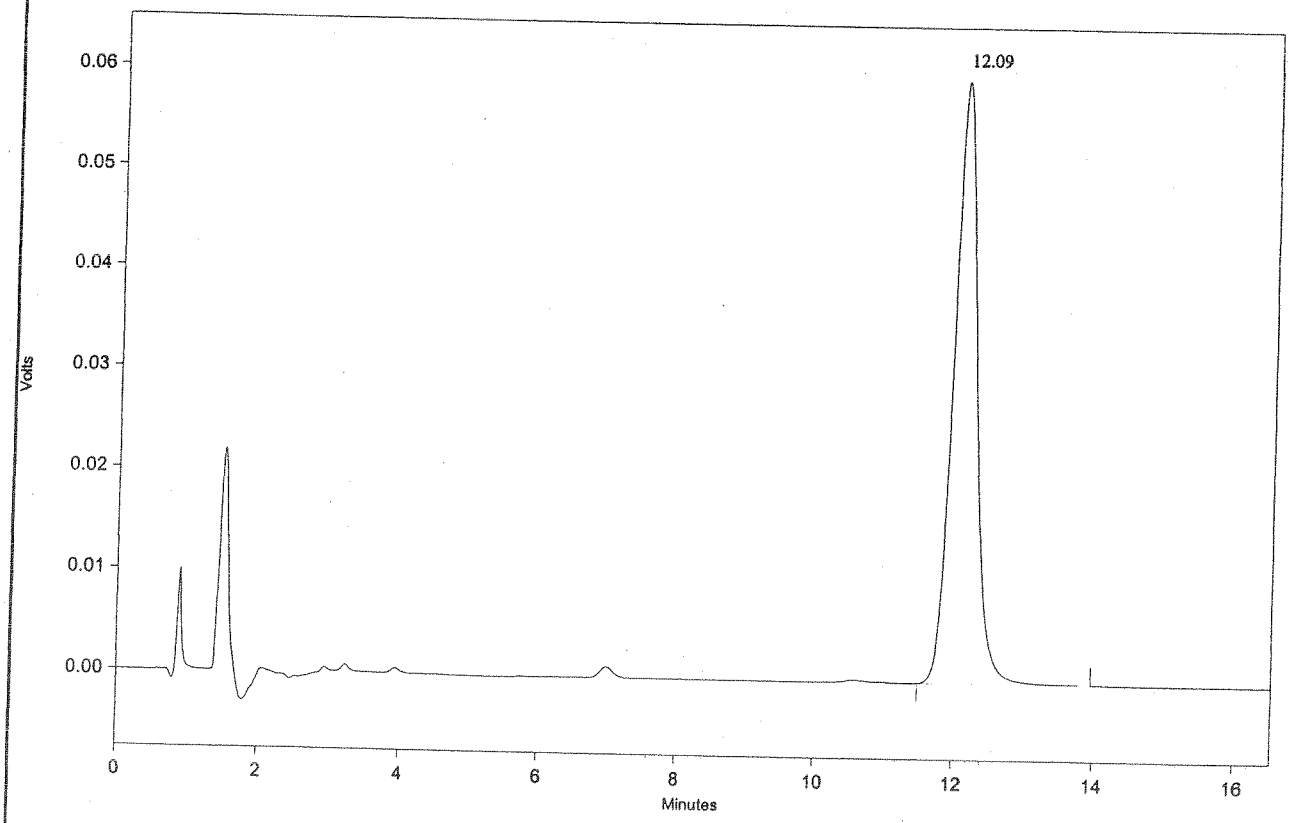


Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

Name: Standard Solution 1 (CCV)
Method: C:\CLASS-VP\METHODS\DigoxinTabs.met
File: C:\CLASS-VP\DATA\DigoxinTabs\454866\Std.Soln.7
Date: 03/11/2008 12:37:05 PM
Vial: 2
Injection Volume: 50 ul

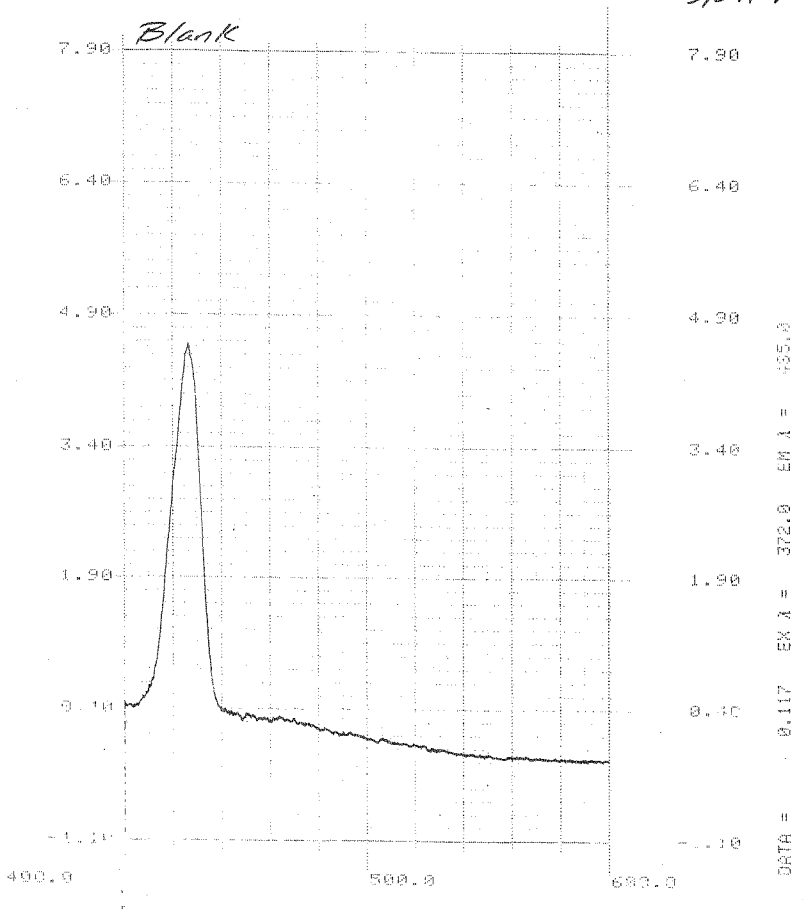
Detector A
(218nm)

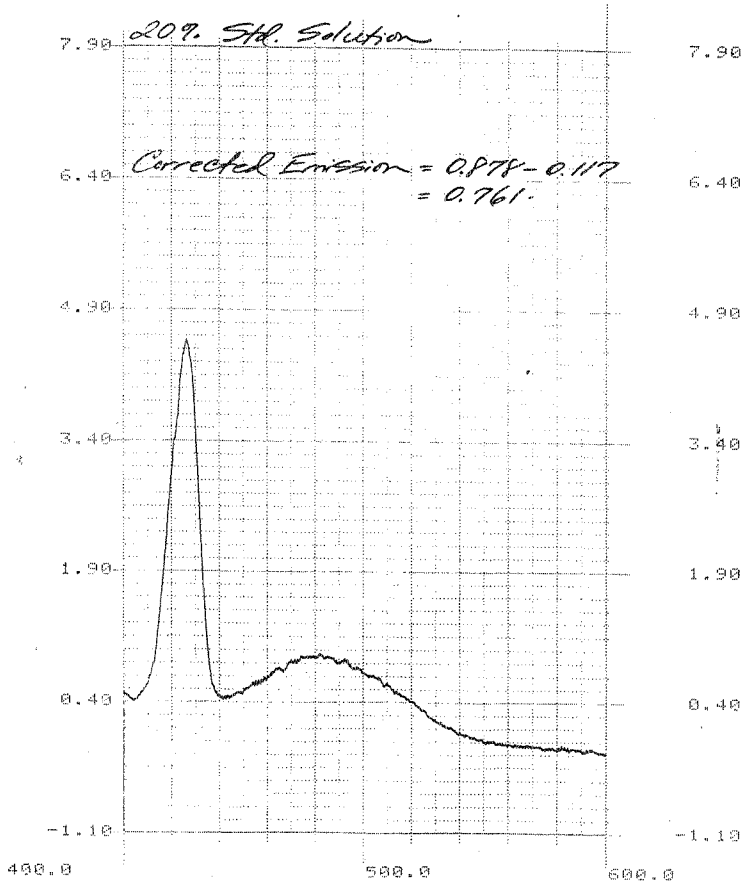
Pk #	Name	Retention Time	Area	Height	Asymmetry	Resolution	Theoretical plates
1	Digoxin	12.09	1367356	59690	1.1	0.0	6590
Totals			1367356	59690			

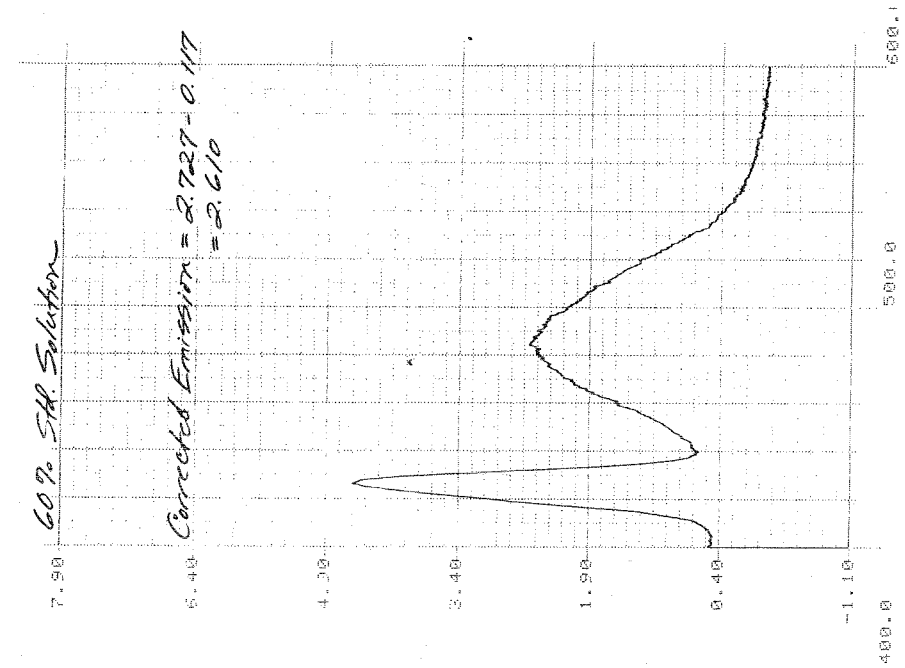


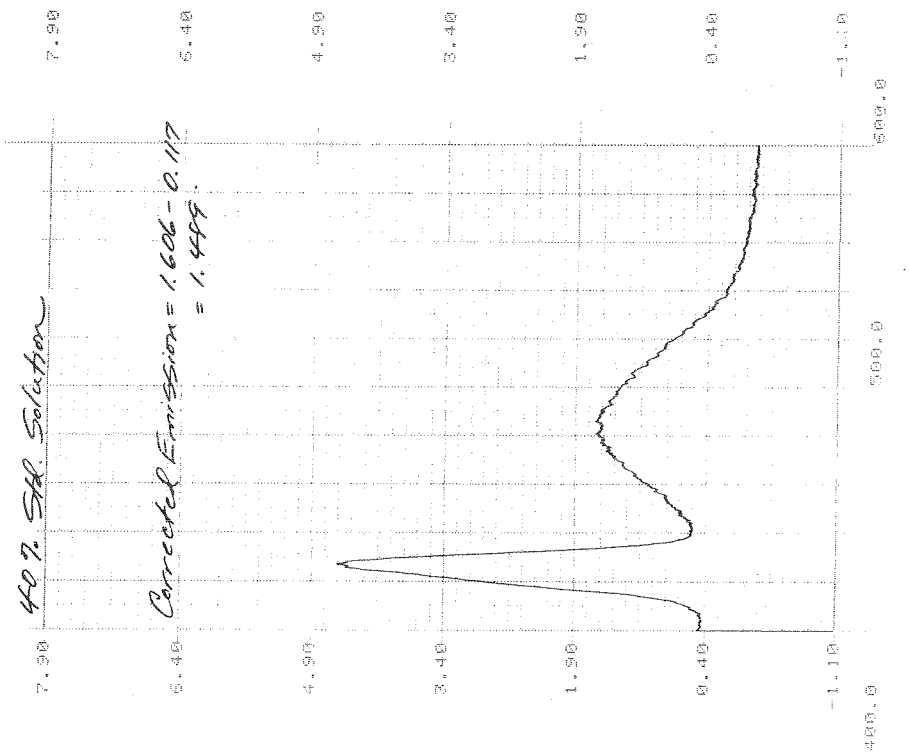
Instrument: Shimadzu HPLC LC-10AT VP, FDA# 5083845 *(QA by V.Fiorella on 1/3/08)*
Analyst: Valentino Fiorella
Mobile Phase: Acetonitrile/Water (26/74)
Flow: 2.0 ml/min.
Column: Supelcosil LC-18-DB *(250 mm x 4.6 mm; 5 um), Serial No. 88682C*

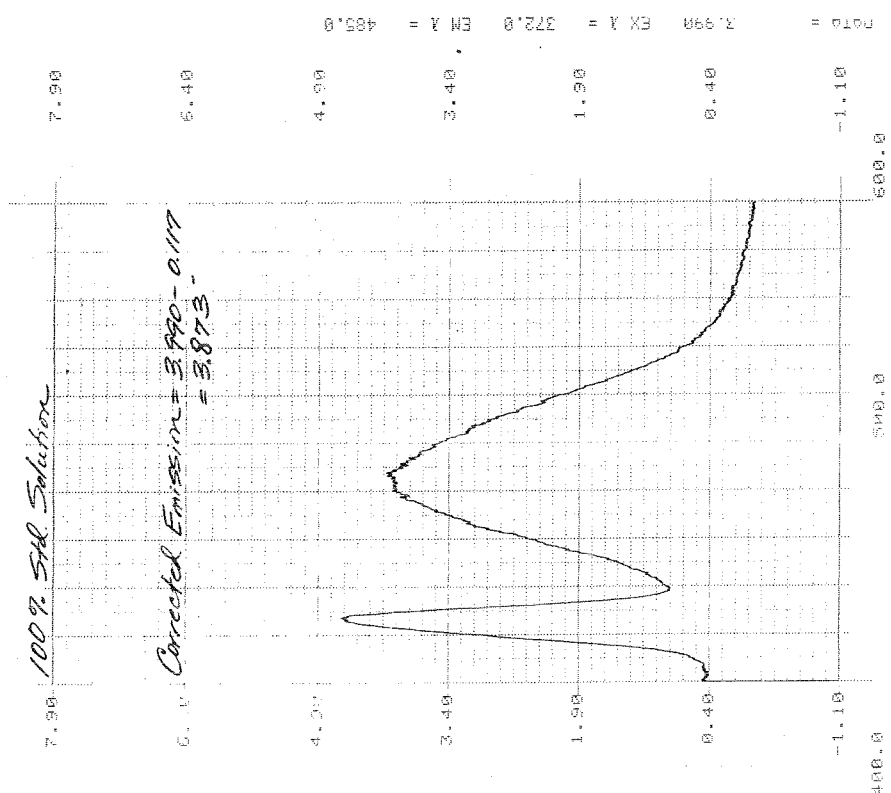
Attachment B
Digoxin Tablets (0.25mg)
Spl. # 454866
5/29/08 VF

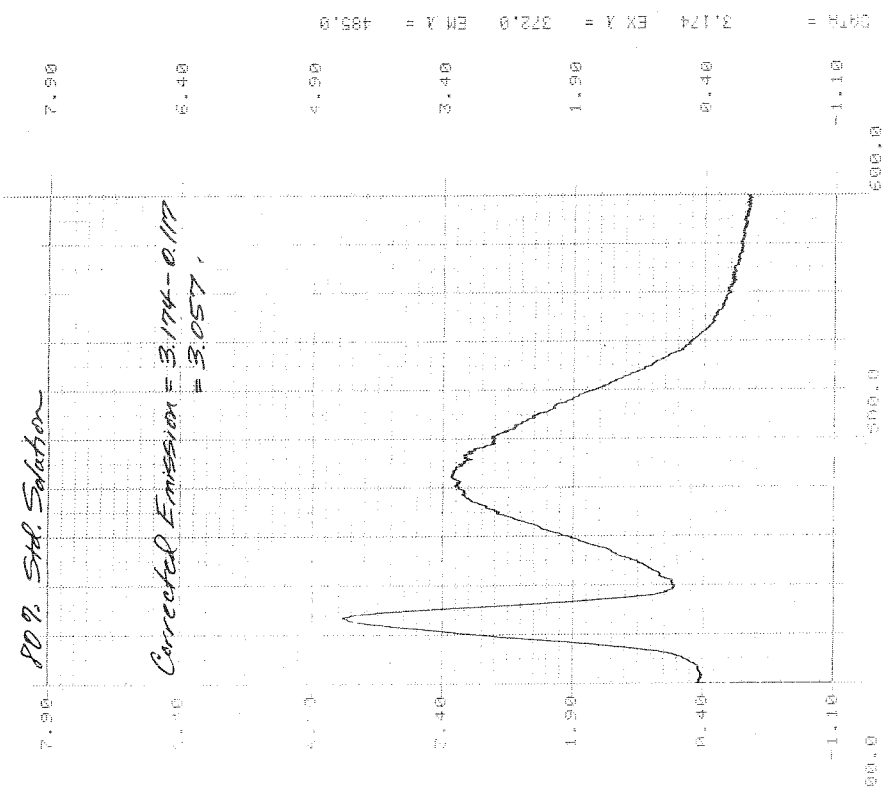


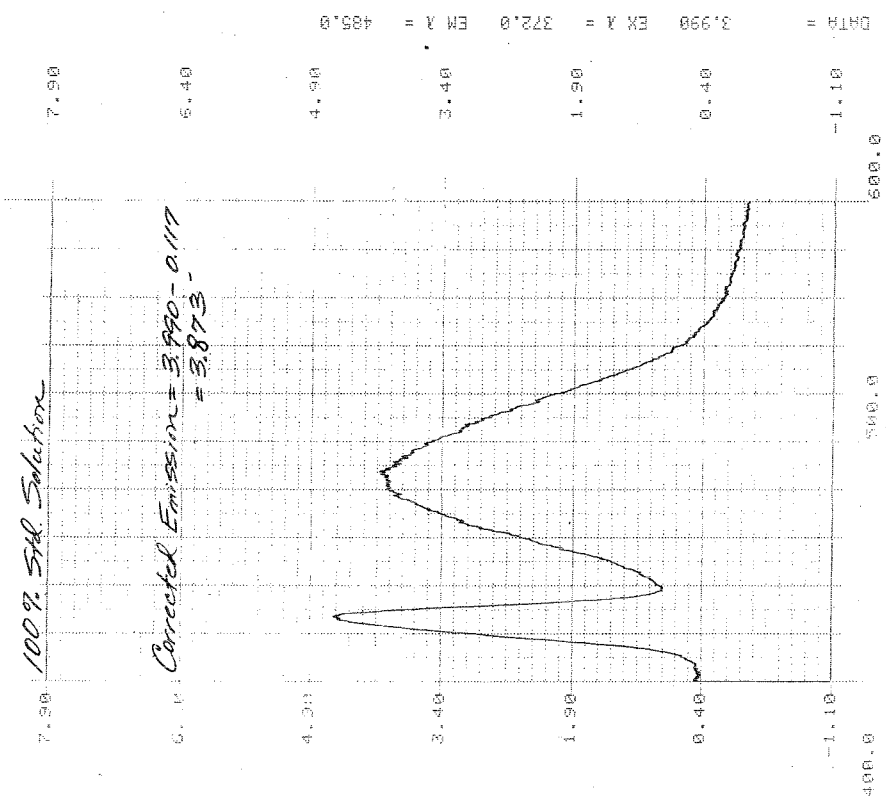


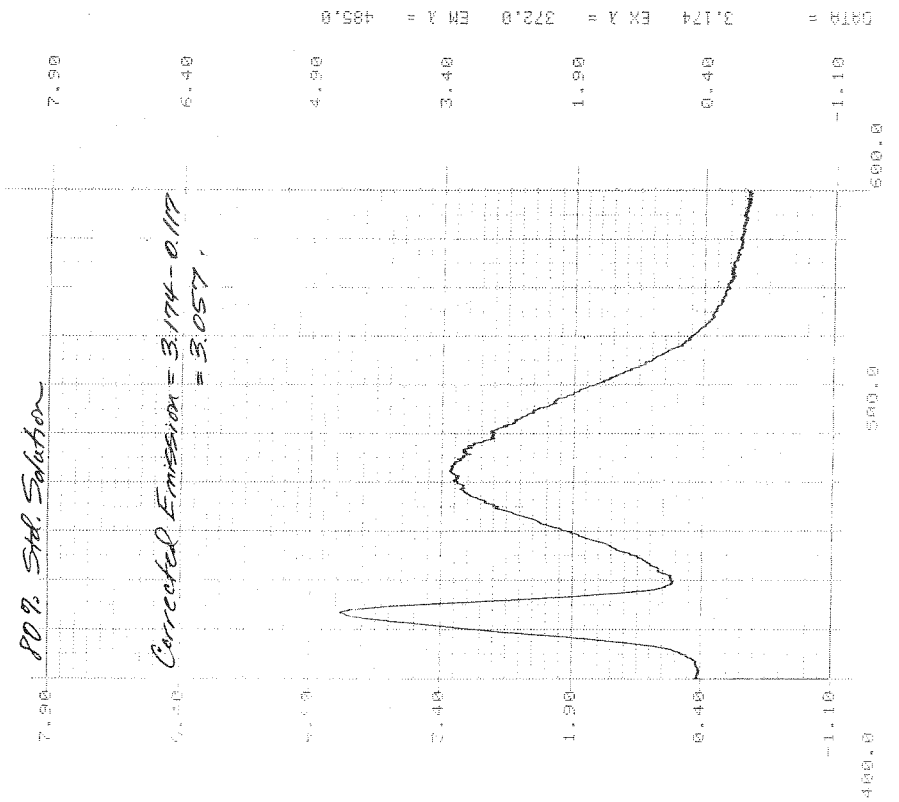

60% Std. Solution
Corrected Emission = 2.727 - 0.117
= 2.610
7.90
5.40
4.90
3.40
1.90
0.40
-1.10
600.0
500.0
400.0

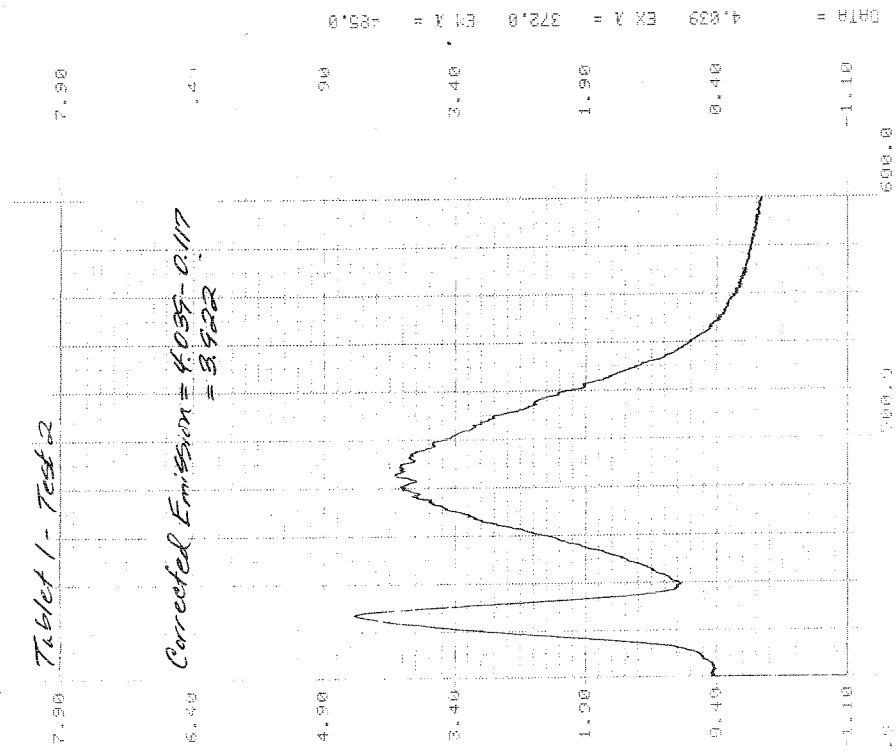

40% Std. Solution
Corrected Emission = 1.604 - 0.117
= 1.487
7.90
5.40
4.90
3.40
1.90
0.40
-1.10
600.0
500.0
400.0

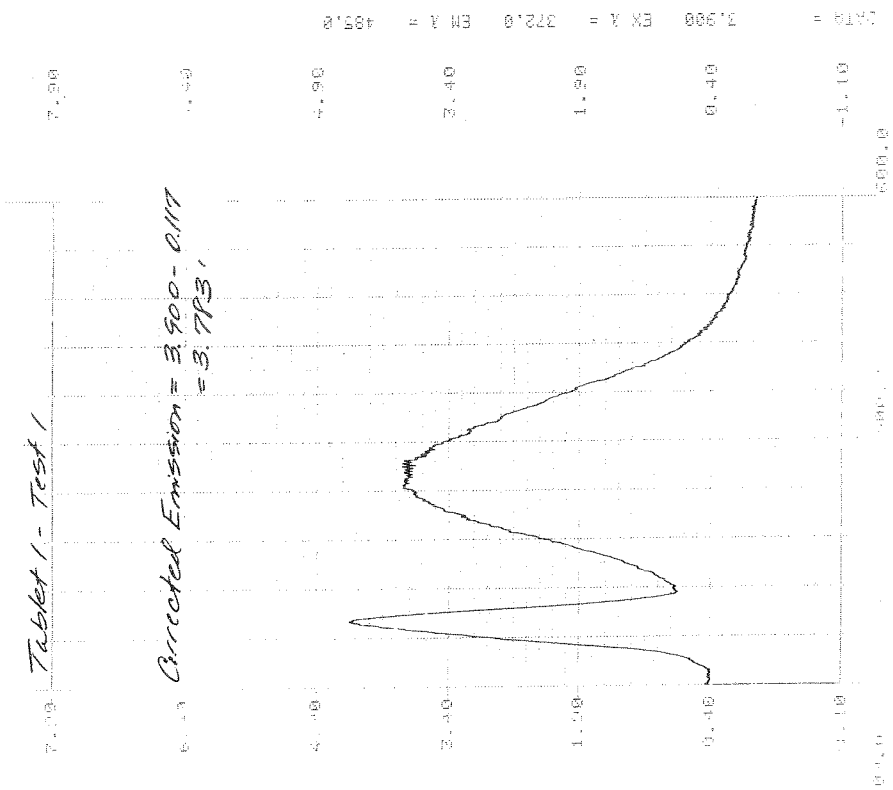

100% Std Solution
Corrected Emission = 3.990 - 0.117
= 3.873
Data = 2.990 EX λ = 372.0 EM λ = 485.0
7.90
6.40
4.90
3.40
1.90
0.40
-1.10
600.0
500.0
400.0

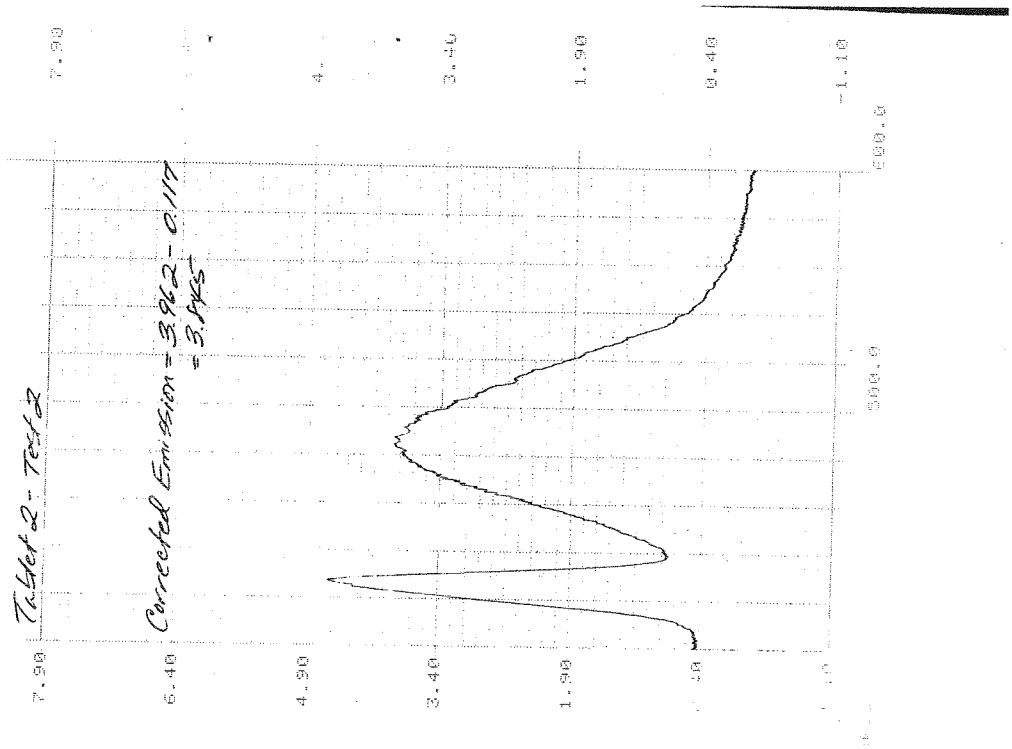

80% Std. Solution
Corrected Emission = 3.174 - 0.117
= 3.057
Data = 3.174 EX λ = 372.0 EM λ = 485.0
7.90
6.40
4.90
3.40
1.90
0.40
-1.10
600.0
500.0
400.0

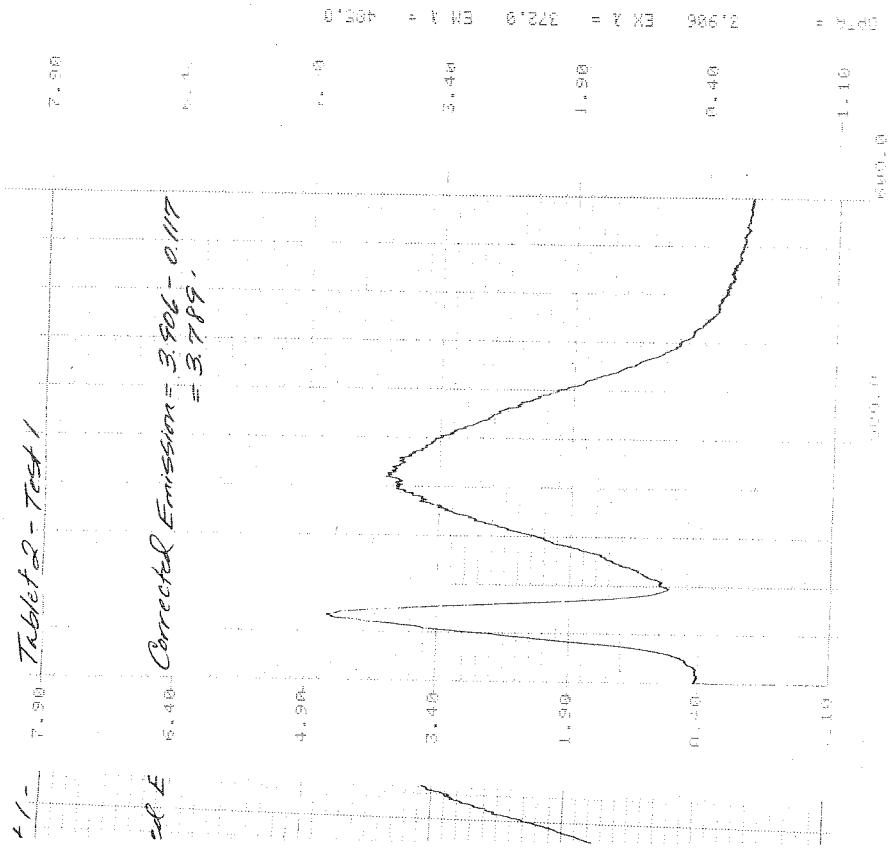

100% Std. Solution
Corrected Emission = 3.990 - 0.117
= 3.873
DATA = 3.990 EX λ = 372.0 EM λ = 485.0
7.90
6.40
4.90
3.40
1.90
0.40
-1.10
600.0
500.0
400.0

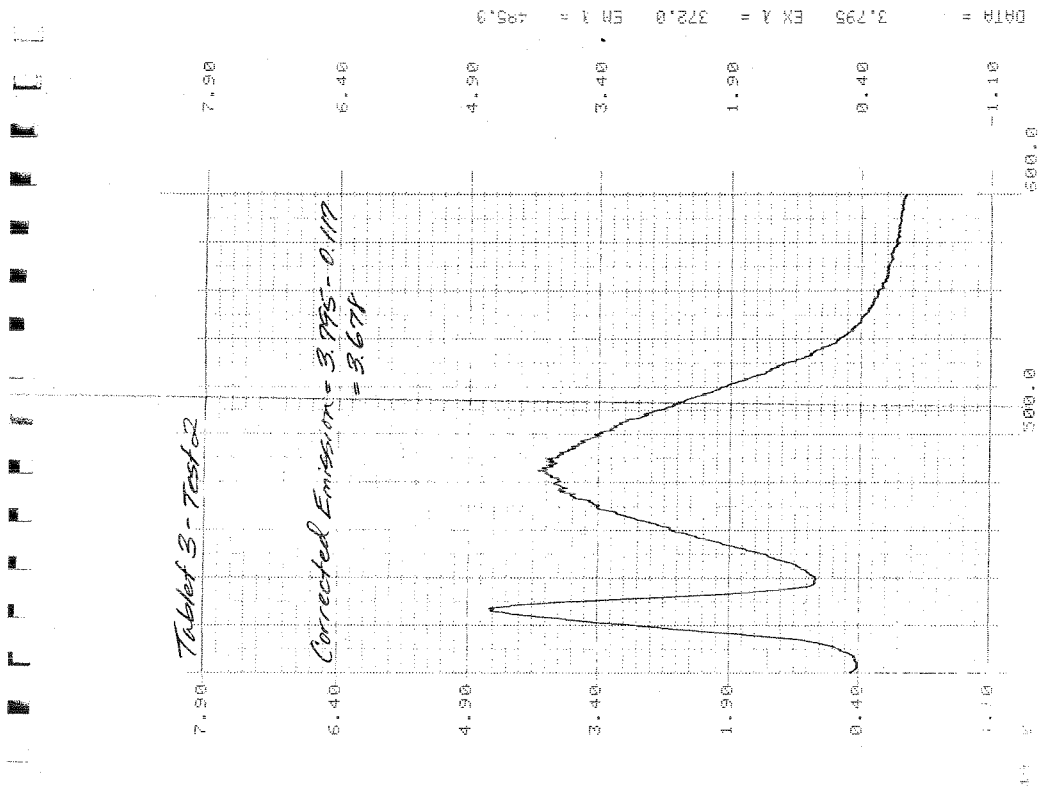

80% Std. Solution
Corrected Emission = 3.174 - 0.117
= 3.057
DATA = 3.174 EX λ = 372.0 EM λ = 485.0
7.90
6.40
4.90
3.40
1.90
0.40
-1.10
600.0
500.0
400.0


Tablet 1 - Test 2
Corrected Emission = 4.035 - 0.117
= 3.920


Tablet 1 - Test 1
Corrected Emission = 3.900 - 0.117
= 3.783


Tablet 2 - Test 2
Corrected Emission = 3.962 - 0.117
= 3.845


Tablet 2 - Test 1
Corrected Emission = 3.906 - 0.117
= 3.789


DATA = 3.795 EX λ = 372.0 EM λ = 495.0
7.90
6.40
4.90
3.40
1.90
0.40
-1.10
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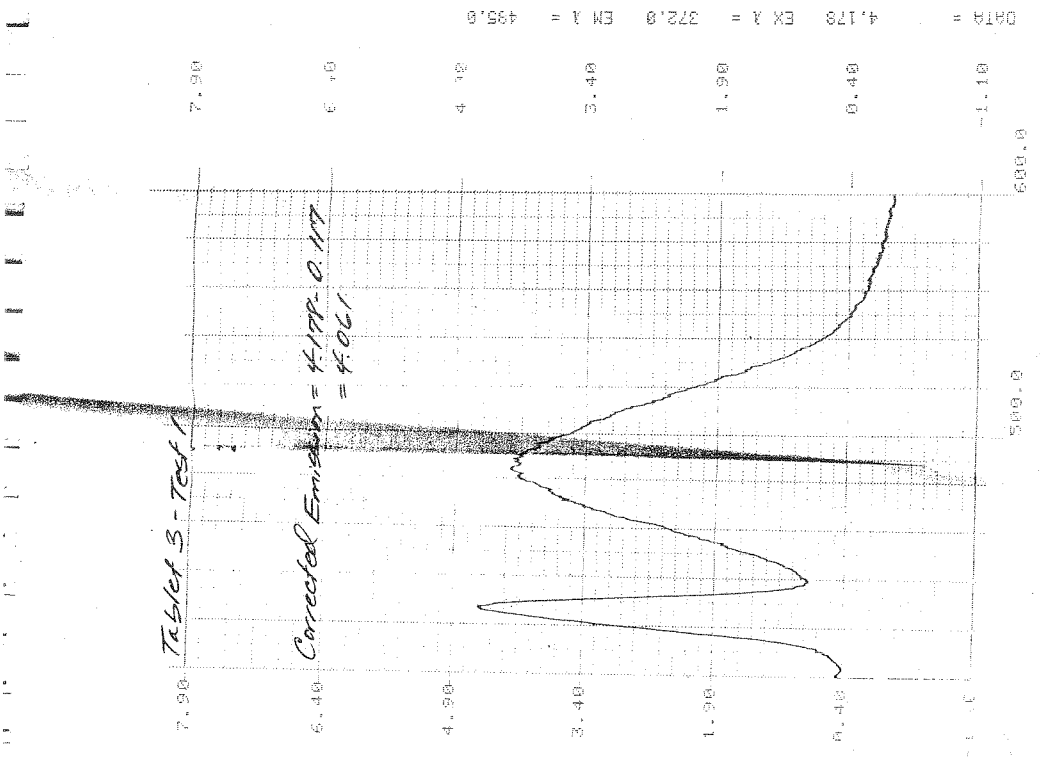
Tablet 3 - Test 02
Corrected Emission = 3.795 - 0.117
= 3.678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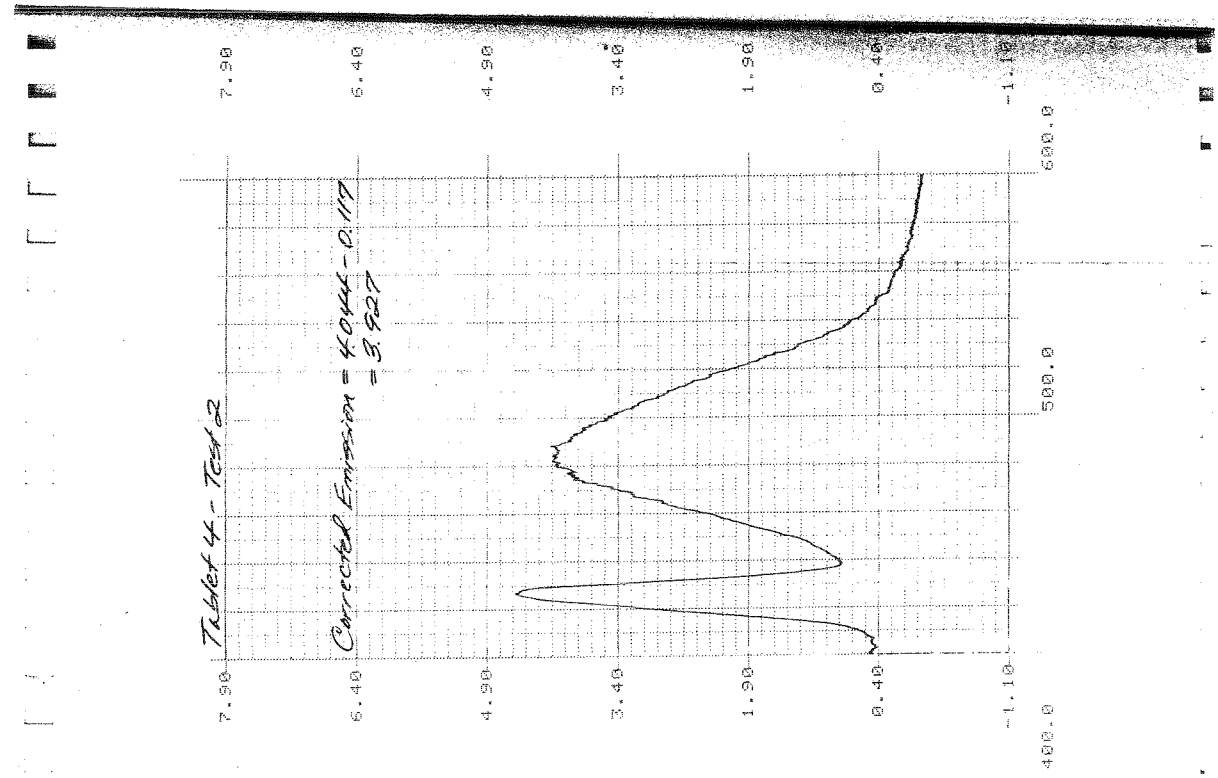
3.40
1.90
0.40
-1.10
500.0
Tablet 3 - Test 1
Corrected Emission = 4.178 - 0.117
= 4.061


Tablet 4 - Test 2
Corrected Emission = 4.044 - 0.119
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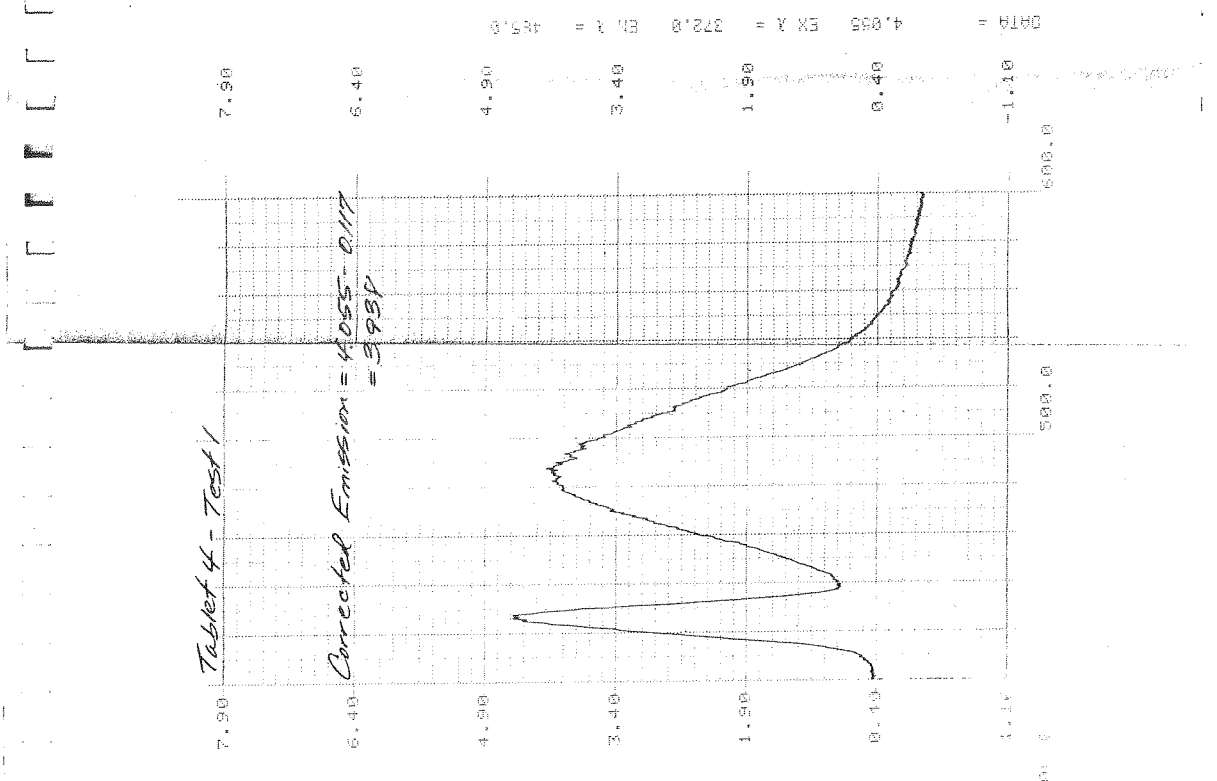
6.40
4.90
3.40
1.90
0.40
-1.10
600.0
500.0
400.0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Tablet 4 - Test 1
Corrected Emission = 4.055 - 0.119
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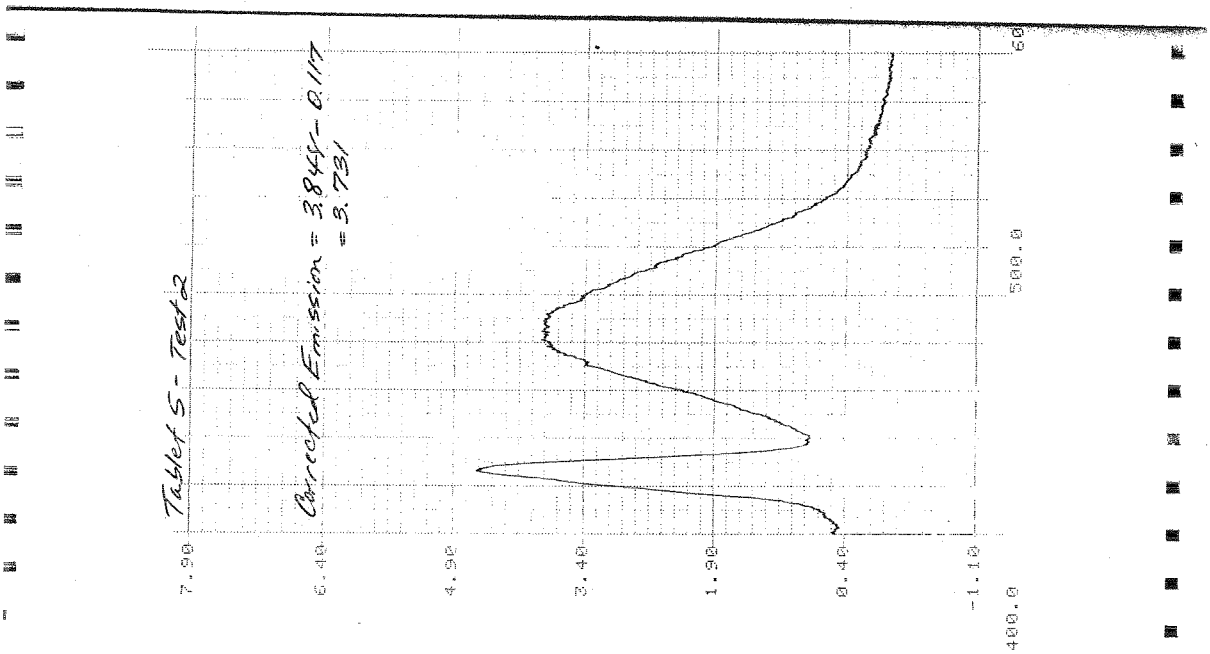
4.90
3.40
1.90
0.40
-1.10
600.0
500.0


Tablet 5 - Test 2
Corrected Emission = 3.845 - 0.117
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6.40
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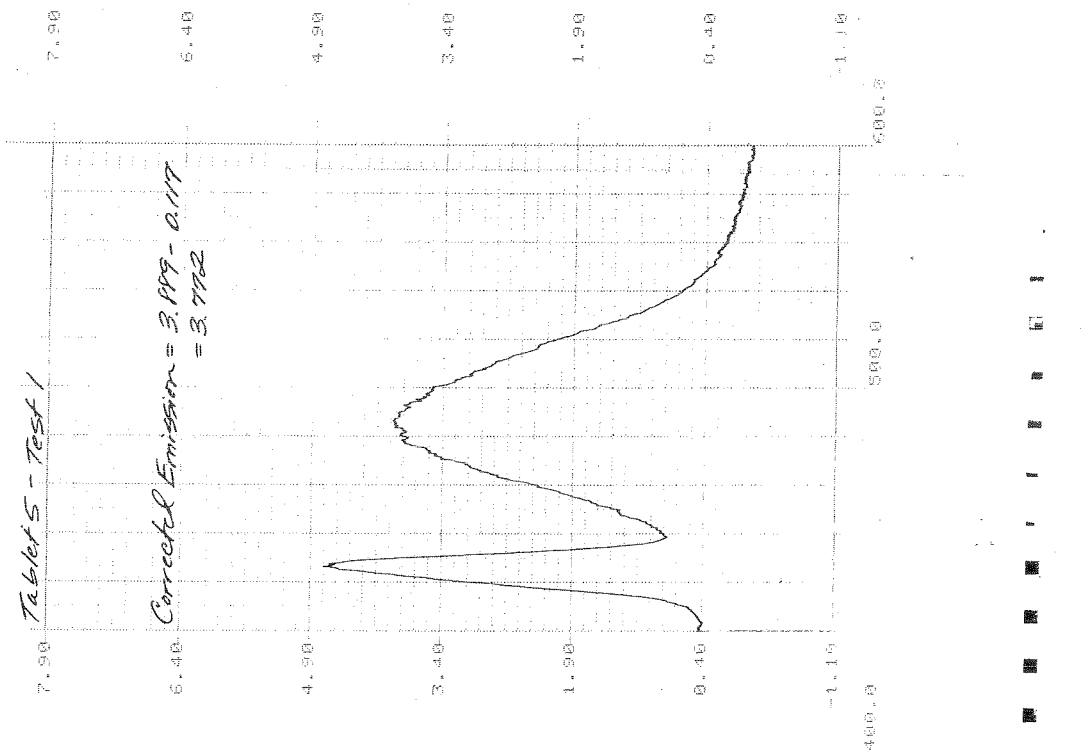
1.90
0.40
-1.10
600.0
500.0
400.0


Tablet 5 - Test 1
Corrected Emission = 3.919 - 0.117
= 3.802
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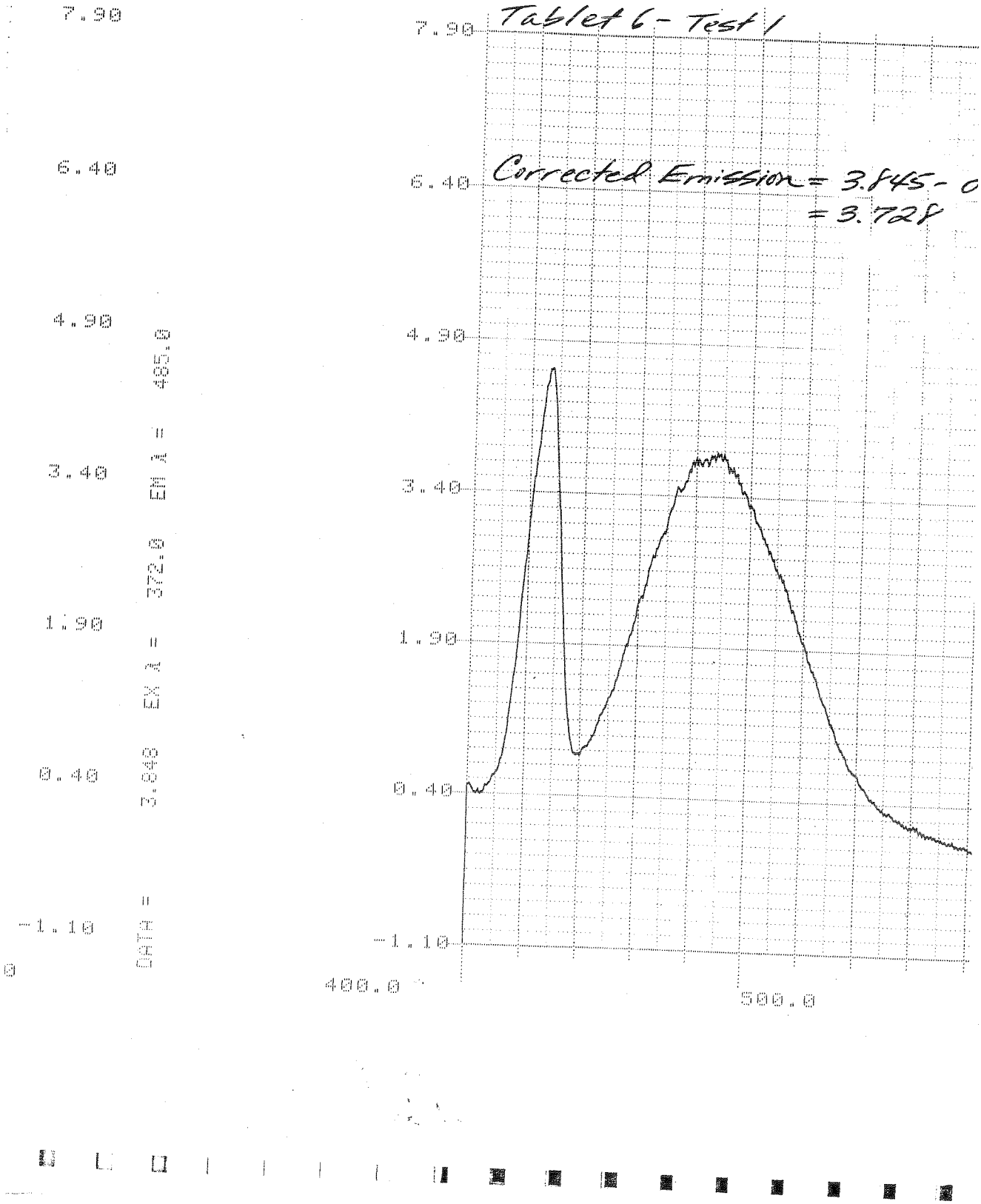
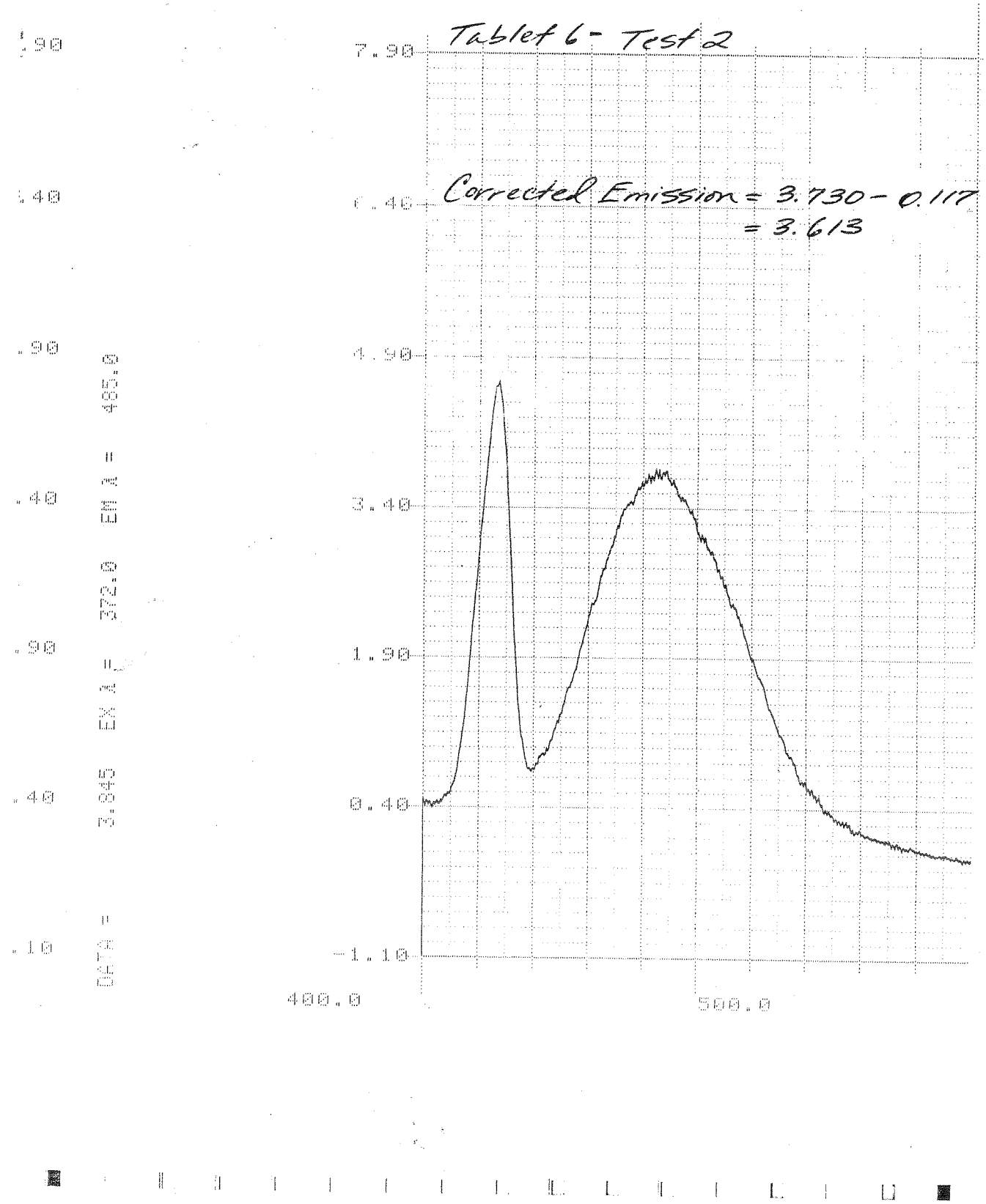
6.40
4.90
3.40
1.90
0.40
-1.10
600.0
500.0
400.0


Tablet 6 - Test 1
Corrected Emission = 3.845 - 0
= 3.728
7.90
6.40
4.90
3.40
1.90
0.40
-1.10
400.0
500.0
EM = 485.0
EX = 372.0
DATA = 7.040


Tablet 6 - Test 2
Corrected Emission = 3.730 - 0.117
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6.40
4.90
3.40
1.90
0.40
-1.10
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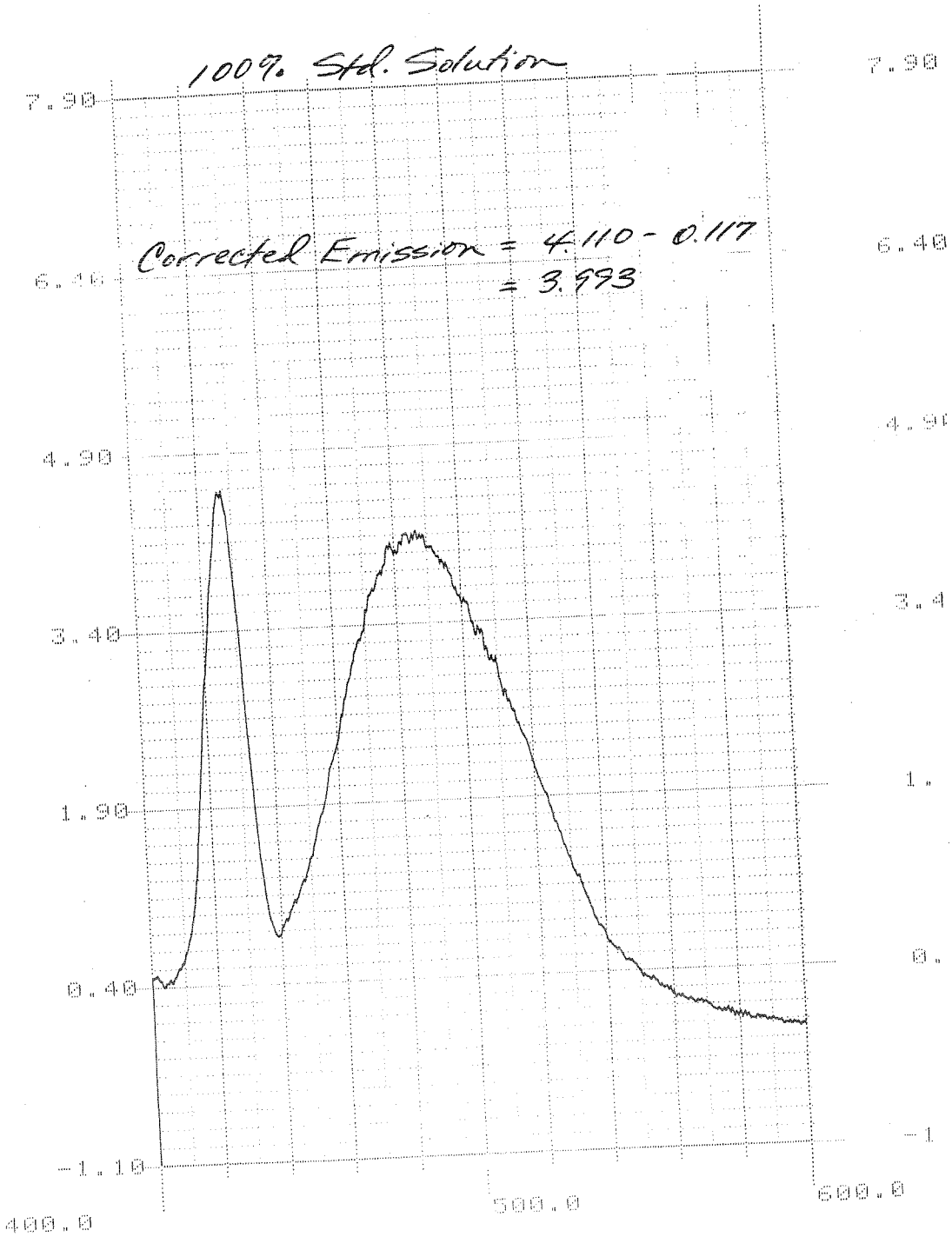
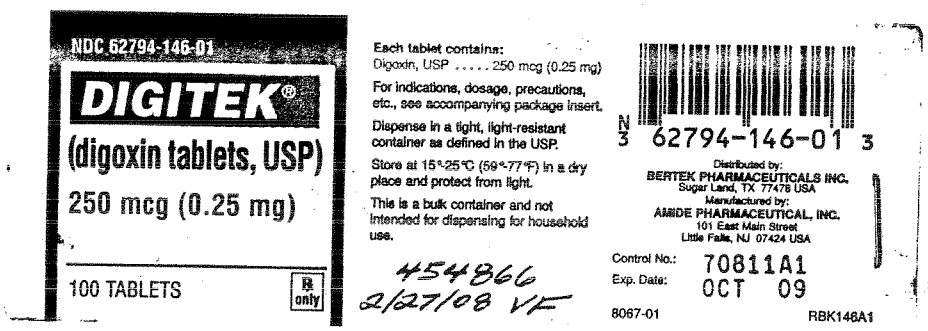
500.0
.90
.40
.90
.40
.10


100% Std. Solution
Corrected Emission = 4.110 - 0.117
= 3.993
7.90
6.40
4.90
3.40
1.90
0.40
-1.10
400.0
500.0
600.0
7.90
6.40
4.9
3.4
1.
0.
-1

Digoxin Tablets (0.25 mg)
Spl.# 454866
2/27/08
VF

Labeling



Labeling

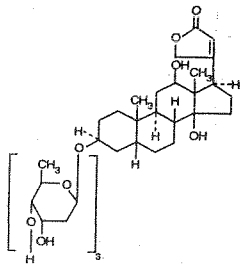
BKDGTK:R4

DIGITEK®
(digoxin tablets, USP)
℞ only

454866 VF 2/27/08

DESCRIPTION: DIGITEK (digoxin) is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a number of plants. Digoxin is extracted from the leaves of *Digitalis lanata*. The term "digitalis" is used to designate the whole group of glycosides. The glycosides are composed of two portions: a sugar and a cardenolide (hence "glycosides").

Digoxin is described chemically as (3 ß, 5 ß, 12 ß)-3-[(*O*-2, 6-dideoxy-ß-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-ß-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-ß-*D*-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-card-20(22)-enolide. Its molecular formula is $C_{41}H_{64}O_{14}$, its molecular weight is 780.94, and the structural formula shown:



Digoxin exists as odorless white crystals that melt with decomposition above 230°C. The drug is practically insoluble in water and in ether; slightly soluble in diluted (50%) alcohol and in chloroform; and freely soluble in pyridine.

DIGITEK is supplied as 125-mcg (0.125-mg) or 250-mcg (0.25-mg) tablets for oral administration. Each tablet contains the labeled amount of digoxin USP and the following inactive ingredients: corn starch, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, lactose monohydrate and anhydrous lactose, silicon dioxide and stearic acid. In addition, the 125-mcg (0.125-mg) tablet contains D&C Yellow No. 10 Aluminum Lake.

CLINICAL PHARMACOLOGY: Mechanism of Action: Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium exchange) an increase in the intracellular concentration of calcium. The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system mediated by effects on the autonomic nervous system. The autonomic effects include: (1) a vagomimetic action, which is responsible for the effects of digoxin on the sinoatrial and atrioventricular (AV) nodes; and (2) baroreceptor sensitization, which results in increased afferent inhibitory activity and reduced activity of the sympathetic nervous system and renin-angiotensin system for any given increment in mean arterial pressure. The pharmacologic consequences of these direct and indirect effects are: (1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); (2) a decrease in the degree of activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal deactivating effect); and (3) slowing of the heart rate and decreased conduction velocity through the AV node (vagomimetic effect). The effects of digoxin in heart failure are mediated by its positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in atrial arrhythmias are related to its vagomimetic actions. In high doses, digoxin increases sympathetic outflow from the central nervous system (CNS). This increase in sympathetic activity may be an important factor in digitalis toxicity.

Pharmacokinetics: ***Absorption:*** Following oral administration, peak serum concentrations of digoxin occur at 1 to 3 hours. Absorption of digoxin from digoxin tablets has been demonstrated to be 60% to 80% complete compared to an identical intravenous dose of digoxin (absolute bioavailability) or Digoxin Solution in Capsules (relative bioavailability). When digoxin tablets are taken after meals, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged. When taken with meals high in bran fiber, however, the amount absorbed from an oral dose may be reduced. Comparisons of the systemic availability and equivalent doses for oral preparations of digoxin are shown in Table 1:

Table 1: Comparisons of the Systemic Availability and Equivalent Doses for Oral Preparations of Digoxin

Product	Absolute Bio-availability	Equivalent Doses(mcg)* Among Dosage Forms			
Digoxin Tablets	60-80%	62.5	125	250	500
Digoxin Pediatric Elixir	70-85%	62.5	125	250	500
Digoxin Solution in Capsules	90-100%	50	100	200	400
Digoxin Injection/IV	100%	50	100	200	400

*For example, 125-mcg Digoxin Tablets equivalent to 125 mcg Digoxin Pediatric Elixir equivalent to 100 mcg Digoxin Solution in Capsules equivalent to 100 mcg Digoxin Injection/IV.

In some patients, orally administered digoxin is converted to inactive reduction products (e.g., dihydrodigoxin) by colonic bacteria in the gut. Data suggest that one in ten patients treated with digoxin tablets will degrade 40% or more of the ingested dose. As a result, certain antibiotics may increase the absorption of digoxin in such patients. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation, and may be as much as two-fold in some cases.

Distribution: Following drug administration, a 6-to 8-hour tissue distribution phase is observed. This is followed by a much more gradual decline in the serum concentration of the drug, which is dependent on the elimination of digoxin from the body. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state post-distribution serum concentrations are in equilibrium with tissue concentrations and correlate with pharmacologic effects. In individual patients, these post-distribution serum concentrations may be useful in evaluating therapeutic and toxic effects (see DOSAGE AND ADMINISTRATION: Serum Digoxin Concentrations).

Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution. Digoxin crosses both the blood-brain barrier and the placenta. At delivery, the serum digoxin concentration in the newborn is similar to the serum concentration in the mother. Approximately 25% of digoxin in the plasma is bound to protein. Serum digoxin concentrations are not significantly altered by large changes in fat tissue weight, so that its distribution space correlates best with lean (i.e., ideal) body weight, not total body weight.

Metabolism: Only a small percentage (16%) of a dose of digoxin is metabolized. The end metabolites, which include 3 ß-digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates, are polar in nature and are postulated to be formed via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

Excretion: Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following intravenous administration to healthy volunteers, 50% to 70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. In healthy volunteers with normal renal function, digoxin has a half-life of 1.5 to 2 days. The half-life in anuric patients is prolonged to 3.5 to 5 days. Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or during cardiopulmonary bypass because most of the drug is bound to tissue and does not circulate in the blood.

Special Populations: Race differences in digoxin pharmacokinetics have not been formally studied. Because digoxin is primarily eliminated as unchanged drug via the kidney and because there are no important differences in creatinine clearance among races, pharmacokinetic differences due to race are not expected.

The clearance of digoxin can be primarily correlated with renal function as indicated by creatinine clearance. The Cockcroft and Gault formula for estimation of creatinine clearance includes age, body weight, and gender. A table that provides the usual daily maintenance dose requirements of digoxin tablets based on creatinine clearance (per 70 kg) is presented in the DOSAGE AND ADMINISTRATION section.

Plasma digoxin concentration profiles in patients with atrial fibrillation generally fell within the range of profiles in subjects.

Pharmacodynamic and Clinical Effects: The time course of macologic effect and to peak effect of preparations is shown in Table 2:

Table 2: Times to Onset of Pharmacologic Effect a of Preparations of Digoxin

Product	Time to Onset of Effect*
Digoxin Tablets	0.5-2 hours
Digoxin Pediatric Elixir	0.5-2 hours
Digoxin Solution in Capsules	0.5-2 hours
Digoxin Injection/IV	5-30 minutes†

*Documented for ventricular response rate in a inotropic effects and electrocardiographic changes †Depending upon rate of infusion.

Hemodynamic effects: Digoxin produces hemodynamic in patients with heart failure. Short- and long-term drug increases cardiac output and lowers pulmonary pulmonary capillary wedge pressure, and systemic ance. These hemodynamic effects are accompanied b the left ventricular ejection fraction and a decrease and end-diastolic dimensions.

Chronic Heart Failure: Two 12-week, double-blin trolled studies enrolled 178 (RADIANCE trial) and 88 patients with NYHA class II or III heart failure previou digoxin, a diuretic, and an ACE inhibitor (RADIANCE domized them to placebo or treatment with digox demonstrated better preservation of exercise capac randomized to digoxin. Continued treatment with digo risk of developing worsening heart failure, as evidence ure-related hospitalizations and emergency care an concomitant heart failure therapy. The larger study treatment-related benefits in NYHA class and pa assessment. In the smaller trial, these trended in favor benefit.

The Digitalis Investigation Group (DIG) main trial w ter, randomized, double-blind, placebo-controlled mor 6,801 patients with heart failure and left ventricular ej ≤0.45. At randomization, 67% were NYHA class I or II, 7 failure of ischemic etiology, 44% had been receiving most were receiving concomitant ACE inhibitor (94%) (82%). Patients were randomized to placebo or digoxi which was adjusted for the patient's age, sex, lean bod serum creatinine (see DOSAGE AND ADMINISTRATION), for up to 58 months (median 37 months). The median d scribed was 0.25 mg. Overall all-cause mortality was difference between groups (95% confidence limits for r 0.91 to 1.07). Digoxin was associated with a 25% red number of hospitalizations for heart failure, a 28% red risk of a patient having at least one hospitalization for h and a 6.5% reduction in total hospitalizations (for any c

Use of digoxin was associated with a trend in reducti all-cause death or hospitalization. The trend was evid groups of patients with mild heart failure as well as mon ease, as shown in Table 3. Although the effect on all-ca hospitalization was not statistically significant, much o ent benefit derived from effects on mortality and hos attributed to heart failure.

Table 3: Subgroup Analyses of Mortality and Hospitaliza the First Two Years Following Randomization.

	n	Risk of All-Cause Mortality or All-Cause Hospitalization*		
		Placebo	Digoxin	Relat
All Patients (EF ≤ 0.45)	6801	604	593	0 (0.8
NYHA I/II	4571	549	541	0 (0.8
EF 0.25-0.45	4543	568	571	0 (0.9
CTR ≤ 0.55	4455	561	563	0. (0.9
NYHA III/IV	2224	719	696	0. (0.8
EF < 0.25	2258	677	637	0. (0.7
CTR > 0.55	2346	687	650	0. (0.7
EF > 0.45†	987	571	585	1. (0.8

reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated exposure of a nursing infant to digoxin via breast feeding will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

Pediatric Use: Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive to the effects of digoxin, and the dosage of the drug must not only be reduced but must be individualized according to their degree of maturity. Digitalis glycosides can cause poisoning in children due to accidental ingestion.

Geriatric Use: The majority of clinical experience gained with digoxin has been in the elderly population. This experience has not identified differences in response or adverse effects between the elderly and younger patients. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, which should be based on renal function, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when digoxin is used within the recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions.

Because some patients may be particularly susceptible to side effects with digoxin, the dosage of the drug should always be selected carefully and adjusted as the clinical condition of the patient warrants. In the past, when high doses of digoxin were used and little attention was paid to clinical status or concurrent medications, adverse reactions to digoxin were more frequent and severe. Cardiac adverse reactions accounted for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions. However, available evidence suggests that the incidence and severity of digoxin toxicity has decreased substantially in recent years. In recent controlled clinical trials, in patients with predominantly mild to moderate heart failure, the incidence of adverse experiences was comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking digoxin compared to 0.9% in patients taking placebo. In this trial, the most common manifestations of digoxin toxicity included gastrointestinal and cardiac disturbances; CNS manifestations were less common.

Adults: Cardiac: Therapeutic doses of digoxin may cause heart block in patients with pre-existing sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable. High doses of digoxin may produce a variety of rhythm disturbances, such as first-degree, second-degree (Wenckebach), or third-degree heart block (including asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm; unifocal or multiform ventricular premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST segment depression which should not by themselves be considered digoxin toxicity. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

Gastrointestinal: Digoxin may cause anorexia, nausea, vomiting and diarrhea. Rarely, the use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines.

CNS: Digoxin can produce visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy, confusion and mental disturbances (such as anxiety, depression, delirium, and hallucination).

Other: Gynecomastia has been occasionally observed following the prolonged use of digoxin. Thrombocytopenia and maculopapular rash and other skin reactions have been rarely observed.

The following table summarizes the incidence of those adverse experiences listed above for patients treated with digoxin tablets or placebo from two randomized, double-blind, placebo-controlled withdrawal trials. Patients in these trials were also receiving diuretics with or without angiotensin-converting enzyme inhibitors. These patients have been stable on digoxin, and were randomized to digoxin or placebo. The results shown in Table 4 reflect the experience in patients following dosage titration with the use of serum digoxin concentrations and careful follow-up. These adverse experiences are consistent with results from a large, placebo-controlled mortality trial (DIG trial) wherein over half the patients were not receiving digoxin prior to

Food and Drug Administration Office of Regulatory Affairs

Collection Report

For Sample Number: 454866

This is an accurate reproduction of the original electronic record as of: 06/05/2008

Flag	Flag Remarks

Episode Number	Origin	Basis	Sample Type	FIS Smpl Num	Status
	Domestic	Surveillance	Official	0885201	Completed

FEI	Date Collected	Product Code	Responsible Firm	PAC	Hours
1610608 2244683	02/15/2008	63FCA06	Manufacturer	56008A	5.5

Compliance Num	Country of Origin
	United States

Related Smpl Num	Position Class	Sampling District	NDC Number	Permit Number	Storage Rqrmnt.
	INV	ATL-DO	62794-146-01		Ambient

Dealer is Consumer	Crx/DEA Schedule	Recall Num	Consumer Compl. Num	Brand Name
No				Bertek Pharmaceuticals Digitek digoxin tablets, USP 250 mcg (0.25 mg)

Product Description
Digitek digoxin tablets, USP 250 mcg (0.25 mg) NDC 62794-146-01

Product Label
See continuation.

Reason for Collection
Sample collected as part of the FY2008 Low-cost Generic Drug Sample Survey (CP 7356.008) FACTS assignment # 896749 ORA concurrence # 2008101702

MFG Codes
70811A1

Expiration Date
10/2009

Firm Legal Name	Address	Type of Firm	Firm FEI	FCE
Mckesson Drug Company	2975 Evergreen Dr Duluth, GA 30096-5843 US	Dealer	1030548	
UDL Laboratories, Inc	12720 Dairy Ashford Rd Sugar Land, TX 77478-2844 US	Manufacturer	1610608	
Actavis Totowa LLC	101 E Main St Little Falls, NJ 07424-5608 US	Manufacturer	2244683	

Size of Lot	Est. Value	Rcpt Type	Carrier Name	Date Shipped
(b) (4) bottles	$ (b) (4)	FDA484		

Description of Sample
Sample consists of 2 bottles, 100 tablets each of Digitek digoxin tablets, USP 250 mcg (0.25 mg)

Method of Collection
Each bottle was collected randomly from the same lot directly from the warehouse line.

How Prepared
See continuation.

Collector's Identification on Package and/or Label
"454866 02/15/08 MMF"

Collector's Identification on Seal
"454866 02/15/08 Myoshi M. Francis"

Sample Delivered To
FedEx

Date Delivered	Orig C/R & Records To
02/20/2008	DAL-DO
Lab w/Split Sample	**Lab**
0	NRL

Food and Drug Administration Office of Regulatory Affairs

Collection Report

For Sample Number: 454866

This is a true reproduction of the original electronic record as of 06/05/2008

Document Number	Document Date	Document Type	Document Remarks

Remarks
See continuation.

Payment Amount	Payment Method	704(d) Sample	702(b) Portion	Collector's Name
(b) (4)	Billed	No	No	Myoshi M Francis

Name of Signer	Date & Time of Signature			Meaning
Myoshi M Francis	02/19/2008	03:22 PM	ET	Collector

Food and Drug Administration
Collection Report
For Sample Number: 454866

Continuation:

Product Label
Each bottle was labeled in part: "NDC 62794-146-01 DIGITEK (digoxin tablets, USP) 250 mcg (0.25 mg) 100 TABLETS Rx only***Each tablet contains: Digoxin, USP 250 mcg (0.25 mg)***Distributed by: BERTEK PHARMACEUTICALS INC. Sugarland, TX 77478 USA Manufactured by: AMIDE PHARMACEUTICALS, INC. 101 East Main Street Little Falls, NJ 07424 USA Control No.: 70811A1 Exp. Date: OCT 09"

How Prepared
Each bottle was identified: "454866 02/15/08 MMF". The bottles were placed in a small plastic bag which was identified as "454866 02/15/08 MMF" and officially sealed "454866 02/15/08 Myoshi M. Francis". Form FDA-525 was attached. Sample was shipped to NRL via FedEx on 02/20/08.

Remarks
The sample was collected on 02/15/2008 and kept under secure supervision by Investigator Meshay Francis. Sample was placed under lock and key and held under ambient conditions until prepared and shipped on 02/20/2008.